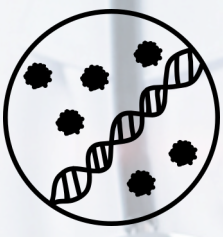
APTI Women's Forum

Newsletter

Orphan and Rare Diseases



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Editor's Note

Prof. Vandana B. Patravale
Chief Editor,
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Dear Readers,

I have been writing the editorial note for APTI Women's forum newsletter since 2020, but this time it gives me immense pleasure to share with you all that we received great response in form of articles from different parts of the nation. Aligning with "The year of Zebra", an ambitious initiative by Elsevier Health we came up with the theme for current APTI women's newsletter as **"Orphan and Rare Diseases".**

2023 marked as the 40th anniversary of the Orphan Drug Act which gave hope to the hundreds of millions of people around the world who are directly affected by rare disorders. Rare diseases, by definition, affect a small percentage of the population, but the impact on those individuals and their families is profound. As we delve into this edition of our newsletter, we focus on the critical and often overlooked topic of orphan drugs and rare diseases.

In the newsletter you will find the details of global prevalence of rare diseases, challenges associated with them, and their psychosocial impact. Brief yet impactful description of rare diseases like rare sclerosis, amyotrophic lateral sclerosis, aplastic anemia, nephrotic syndrome, Rasmussen's Encephalitis, sleep paralysis, *Gilles de la Tourette* syndrome, Moebius syndrome, Progeria syndrome, cystic fibrosis, ocular rare diseases, omphalitis, etc. Also, there are articles describing utilization of artificial intelligence in the field of rare diseases like conducting in silico clinical trials. Overall the newsletter comprises of both general and specific articles which we hope will ignite the minds of readers.

The editorial board is certain that you will get equal interest from reading this subject issue as you did from reading our prior APTI Women Forum Newsletters. We express our utmost gratitude to all the authors for their diligent work in making this newsletter very enlightening. I express my gratitude to the whole editorial team for their tireless efforts, which included both the conceptualization and editing of the reviews provided by authors from different parts of the country. I would like to convey my thanks and gratitude to Prof. Suneela Dhaneshwar, Prof. Vanaja K, Dr. Jubie Selvaraj, Dr. Rashmi Trivedi, Dr. Emmanuel Chukwuebuka Umeyor, Dr. Madhavi Bhavaraju, Dr. Rakhi Khabiya, Dr. Pooja Chawla, Prof. Indu Pal Kaur, Dr. Preeti Suresh, and Dr. Shubhini Saraf for providing editorial comments to the articles.

Also, I wish to thank VBP research group, specially Sarika Jadhav, Preeya Negi, and Diksha Narula for all the support rendered for this newsletter.

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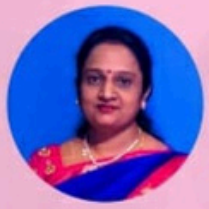

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Exploring the landscape of orphan and rare diseases


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1. Introduction

Global health care is getting closer to reality by the efforts of numerous national government and non-governmental organisations, as well as international organisations like the World Health Organisation (WHO) and the United Nations Children's Fund. The major global health challenges were to develop the strategies for treating orphan and rare disease.

The terms "orphan diseases" and "rare diseases" are often used interchangeably, but they have slightly different connotations. “Rare diseases" refer to those medical conditions which affect a small percentage of the population. In the United States, a disease is considered rare if it affects fewer than 200,000 people (1). However, definitions of rare diseases may vary by country, while orphan diseases specifically refer to rare diseases that have been neglected by the medical and pharmaceutical industries. The term "orphan" originally came from the lack of attention these diseases received, akin to orphaned children who lacked support and care. The development of treatments for orphan diseases was historically limited due to the small number of patients affected, making them unprofitable for pharmaceutical companies and moreover the pharmaceutical companies also showed little interest in developing treatments for these conditions because they were not financially viable. However, in recent years, there has been growing awareness and efforts to address the needs of patients with rare diseases. Governments, advocacy groups, and research organizations have been working to promote research, increase funding, and develop policies to support the development of therapies for orphan diseases.

The concept of orphan diseases, or rare diseases, gained attention in the 1970s when patients and advocacy groups began to raise awareness about the lack of research, funding, and treatments for these conditions. The term "orphan disease" was coined to reflect the neglected status of these disorders, likening them to orphaned children who lacked support and attention (2,3).

The laws pertaining to orphan drugs differ among industrialised nations and were initially implemented in the US in 1983, Singapore in 1991, Japan in 1993, Australia in 1997, and the EU in 2000 (4). Rare diseases, also referred to as orphan diseases are medical conditions that affect a small percentage of the population. The rare disease according to US definition is one that affects less than 200,000 individuals, the corresponding number in Australia is 2000 and in Japan is 50000 (5). While each rare disease individually affects a small number of people, collectively they impact millions worldwide. These diseases often pose significant challenges for patients and their families due to the lack of effective treatments, limited understanding, and difficulty in diagnosis.

The Orphan Drug Act of 1983 in the United States was a landmark piece of legislation aimed at incentivizing pharmaceutical companies to develop treatments for rare diseases. Before this act, there was little economic incentive for drug companies to invest in researching and developing therapies for diseases that affected only a small number of individuals. The Orphan Drug Act provided financial incentives, such as tax credits and marketing exclusivity, to encourage companies to pursue orphan drug development. The Orphan Drug Act was a turning point in the history of orphan diseases, leading to increased research and development efforts for rare conditions. It helped to bring attention to the unique challenges faced by patients with rare diseases and paved the way for the development of treatments for many previously neglected disorders.

Since the advent of the Orphan Drug Act, there has been significant progress in the field of rare diseases. Advances in genetics, molecular biology, and medical technology have improved our understanding of many rare conditions, leading to earlier diagnosis and the development of targeted therapies. Furthermore, patient advocacy groups have played a vital role in raising awareness, supporting research, and providing resources for individuals and families affected by rare diseases.

Despite these efforts, many challenges remain including diagnosis, which can be a long and frustrating process, often involving visits to multiple specialists and numerous tests. Additionally, once diagnosed, patients may struggle to access appropriate medical care and treatments due to limited availability or high costs.

Furthermore, because these diseases are often poorly understood, there may be a lack of information and resources for patients and their families. Support groups and some organizations play a crucial role in giving support, providing education and resources to individuals affected by rare diseases. Overall, while progress has been made in addressing the needs of patients with rare diseases, much more work is needed to improve diagnosis, treatment, and support for those living with these conditions.

The Orphan Drug Act of 1983 in the United States was instrumental in incentivizing the development of treatments for orphan diseases by providing financial incentives to pharmaceutical companies. There are thousands of rare diseases affecting individuals worldwide. Each rare disease presents its own set of challenges in terms of diagnosis, treatment, and management, often requiring specialized care and support from healthcare professionals and advocacy groups.Some rare diseases and the specific disorders are listed in Table 1.

Table 1. List of some rare diseases and their specific disorders

RARE DISEASES RELATED TO GENETIC DISORDERS	
Huntington's Disease	Muscle coordination is affected in this genetic neurodegenerative disorder which leads to cognitive decline and psychiatric problems. It's caused by a mutation in the HTT gene.
Cystic Fibrosis	A genetic disorder that affects the lungs and digestive system, causing difficulty in breathing and poor growth. It's caused by mutations in the CFTR gene
Pompe Disease	Caused by mutations in the GAA gene, leading to a deficiency of the enzyme acid alpha-glucosidase (GAA) in this genetic disorder. It results in the buildup of glycogen in tissues, particularly in muscles, leading to muscle weakness and other symptoms
Gaucher Disease	A genetic disorder caused by mutations in the GBA gene, leading to a deficiency of the enzyme glucocerebrosidase. It results in the accumulation of certain lipids in cells, particularly in the spleen, liver, and bone marrow, leading to symptoms such as enlargement of these organs, anaemia, and bone problems.
Progeria (Hutchinson-Gilford Progeria Syndrome)	This rare genetic condition causes rapid aging in children, leading to features such as premature aging of the skin, hair loss, joint abnormalities, and cardiovascular problems.
Fibrodysplasia Ossificans Progressiva (FOP)	FOP is an exceedingly rare hereditary condition characterised by the progressive formation of bone outside the skeleton (heterotopic ossification) from muscle and connective tissue. This procedure impairs mobility and may result in serious impairment.
Niemann-Pick Disease	It is a group of rare genetic disorders characterized by the abnormal accumulation of lipids (fats) in cells throughout the body. Symptoms vary depending on the type of Niemann-Pick disease but may include hepatosplenomegaly (enlargement of the liver and spleen), neurological problems, and respiratory difficulties.
RARE DISEASES RELATED TO METABOLIC DISORDERS	
Alkaptonuria	A rare metabolic disorder caused by a deficiency of the enzyme homogentisate-1,2-dioxygenase, which leads to the accumulation of homogentisic acid, which can cause darkening of the urine, joint problems, and other health issues.
Gaucher Disease	It is caused by a deficiency of an enzyme called glucocerebrosidase. This enzyme deficiency leads to the accumulation of a type of fat molecule called glucocerebroside within cells, particularly in the spleen, liver, and bone marrow.
Niemann-Pick Disease	It is caused by the deficiency of an enzyme called acid sphingomyelinase (ASM), leading to the accumulation of sphingomyelin within cells, particularly in the liver, spleen, and brain.

Fabry disease	Characterized by the deficiency of an enzyme called alpha-galactosidase A, leading to the buildup of fatty substances in various organs, causing symptoms such as pain, skin lesions, kidney problems, and cardiovascular complications.
Wilson disease	Characterized by the deficiency of an enzyme called alpha-galactosidase A, leading to the buildup of fatty substances in various organs, causing symptoms such as pain, skin lesions, kidney problems, and cardiovascular complications.
RARE DISEASE RELATED TO AUTOIMMUNE DISORDERS	
Wegener's Granulomatosis	It is a rare autoimmune disorder characterized by inflammation of blood vessels, leading to damage in various organs such as the lungs, kidneys, and upper respiratory tract.
Systemic Lupus Erythematosus (SLE)	A chronic autoimmune disease affecting multiple organs, causing inflammation and tissue damage throughout the body.
Scleroderma	Characterized by excessive collagen production, leading to thickening, and hardening of the skin and connective tissues, a rare autoimmune disorder.
Behçet's Disease	It is a rare autoimmune disorder characterized by recurrent inflammation of blood vessels, resulting in oral and genital ulcers, skin lesions, and eye inflammation.
Kawasaki Disease	This rare autoimmune disorder primarily affects children and causes inflammation of blood vessels throughout the body, leading to symptoms like rash, high fever, redness, swollen lymph nodes, and swelling of the hands and feet.
RARE DISEASES RELATED TO NEUROLOGICAL DISORDERS	
Amyotropic Lateral Sclerosis (ALS)	Also known as Lou Gehrig's disease, is a progressive neurodegenerative disease which affects nerve cells of the brain and spinal cord, leading to muscle weakness with paralysis.
Narcolepsy	A neurological disorder characterized by excessive daytime sleepiness and sleep attacks, with sudden loss of muscle tone (cataplexy). It's thought to be caused by a combination of genetic and environmental factors
Guillain-Barré Syndrome (GBS)	It is a rare neurological disorder where peripheral nerves are attack by the body's immune system causing muscle weakness, numbness, and, in severe cases, paralysis. It often follows a viral or bacterial infection and can lead to life-threatening complications if not treated promptly.
Spinocerebellar Ataxia (SCA)	It refers to a group of inherited neurological disorders characterized by progressive degeneration of the cerebellum and spinal cord, leading to problems with coordination and balance. Symptoms typically include gait ataxia, dysarthria, and may involve other neurological impairments such as tremors and muscle stiffness.

RARE CANCER DISEASES	
Mesothelioma	It is a rare disorder that initially affects the lining of the lungs but may also occur in the lining of the abdomen or heart. It is mostly caused by exposure to asbestos and is associated with symptoms like chest pain, shortness of breath, and weight loss.
Pancreatic Neuroendocrine Tumors (PNETs)	These are rare tumours that develop from neuroendocrine cells in the pancreas and can be non-functional or produce hormones. Symptoms vary widely but may include abdominal pain, jaundice, diarrhoea, and hormonal imbalances.
Chordoma	It is a rare type of bone cancer that typically occurs in the bones of the skull base or spine, arising from remnants of the notochord. Symptoms may include localized pain, neurological deficits, and problems with bladder or bowel function.
Burkitt Lymphoma	It is an aggressive type of non-Hodgkin lymphoma characterized by rapidly growing tumours in the lymph nodes, bone marrow, and other organs. It is associated with Epstein-Barr virus infection and typically presents with symptoms such as swollen lymph nodes, abdominal pain, and fever.
Adrenocortical Carcinoma	It is a rare and aggressive cancer that develops in the adrenal cortex, often causing hormonal imbalances and symptoms such as abdominal pain, weight loss, and high blood pressure.
RARE INFECTIOUS DISEASES	
Creutzfeldt-Jakob Disease (CJD)	It is a rare and rapidly progressive neurological disorder caused by abnormal prion proteins, leading to cognitive decline, involuntary movements, and eventually death within months to years of onset.
RARE PEDIATRIC DISEASES	
Batten Disease	It refers to a group of rare genetic neurodegenerative disorders affecting children, characterized by progressive loss of cognitive and motor function, vision impairment, seizures, and premature death. Also known as neuronal ceroid lipofuscinosis (NCL).
Neurofibromatosis Type 1	It is a genetic disorder causing tumours to grow on nerves throughout the body, leading to various complications such as skin changes, bone deformities, and neurological problems.
Alagille Syndrome	It is a rare genetic disorder affecting the liver, heart, and other organs, characterized by bile duct abnormalities, leading to liver damage and bile flow issues. Symptoms include jaundice, heart murmurs, and skeletal abnormalities.
Aicardi-Goutières Syndrome	It is a rare genetic disorder characterized by neurological and autoimmune symptoms, including progressive brain damage, abnormal brain calcifications, and elevated levels of interferon in the blood.

These are just a few examples, and there are many more rare diseases affecting people around the world. Each of these diseases presents unique challenges for patients and their families, including difficulties in diagnosis, limited treatment options, and the need for specialized care.

2. Orphan and rare diseases: Indian scenario

In India, the understanding and recognition of orphan and rare diseases have evolved over time. Historically, these diseases received little attention due to their low prevalence and the focus on more common health issues. However, awareness about rare diseases and the need for specialized care and support have been gradually increasing in India. It is difficult to develop orphan drugs due to inadequate financial and scientific resources and insufficient subjects to run clinical trials (6).

2.1 Early recognition

In the past, rare diseases were often misdiagnosed or undiagnosed in India due to limited awareness among healthcare professionals and the public. Many patients with rare diseases faced challenges in accessing appropriate medical care and support services

2.2 Emergence of patient's advocacy groups

Over the years, patient advocacy groups and non-profit organizations have played a crucial role in raising awareness about rare diseases in India. These organizations have worked to provide support, information, and resources to individuals and families affected by rare diseases, as well as advocating for better healthcare policies and funding for research and treatment.

2.3 Government initiatives

The Indian government has taken steps to address the needs of individuals with rare diseases. The National Policy for Treatment of Rare Diseases, launched by the Ministry of Health and Family Welfare in 2017, aimed to provide financial support for the treatment of rare diseases through the Rashtriya Arogya Nidhi (RAN) scheme. However, the implementation of this policy has faced challenges, including funding constraints and the need for clearer guidelines and criteria for eligibility.

2.4 Research and collaboration

Efforts to enhance research and collaboration in the field of rare diseases have been ongoing in India. Academic institutions, research organizations, and healthcare professionals have been involved in studies aimed at understanding the genetic basis of rare diseases developing diagnostic tools, and exploring potential treatments.

2.5 Challenges and opportunities

Despite progress, challenges remain in addressing the needs of individuals with rare diseases in India. These challenges include limited access to specialized healthcare services, high treatment costs, lack of awareness among healthcare professionals, and the need for better coordination and collaboration among stakeholders.

2.6 International cooperation

India has also participated in international collaborations and initiatives aimed at advancing research and treatment for rare diseases. Collaboration with global organizations, research institutions, and pharmaceutical companies has helped facilitate knowledge sharing, capacity building, and access to innovative therapies.

Overall, while significant strides have been made in recognizing and addressing the challenges of orphan and rare diseases in India, there is still much work to be done to ensure that individuals with rare diseases receive timely diagnosis, appropriate treatment, and comprehensive support. Continued efforts from all stakeholders, including government agencies, healthcare providers, patient advocacy groups, and the private sector, are essential to improving the lives of those affected by rare diseases in India.

A patient who suffers from rare diseases have an equal right to the medications as those who have common diseases. To follow tis and as per the National Policy on Rare Diseases, the Central Government provides financial support up to Rs. 15 lakhs under the Rashtriya Arogya Nidhi Umbrella Scheme for the treatment of rare diseases that need only one therapy.

3. Conclusion

The US-FDA has continuously made advances and improved the regulatory pathways after accepting the Orphan Drug Act, particularly, in clinical trials which have been successful in some cases. Recently, India has implemented regulations and policies that have impacted the ecosystem of rare diseases, which has long been neglected. According to WHO list of essential medicine, the proportion of orphan drugs in the essential medicine lists increased from 1.9 % (4 /208) in 1977 to 14.6% (70 /478) in 2021 (7). Orphan drugs constitute a unique class of pharmaceuticals in this sense since, in the absence of incentives and legislation pertaining specifically to orphan drugs, their development and marketing would not proceed.

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Navigating the maze of ocular rare diseases


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1. Introduction

Rare ocular diseases present a significant challenge within the public health landscape. Unlike common eye disorders such as near and farsightedness, cataracts, and macular degeneration, these rare maladies are characterised by diagnostic hurdles and dearth of established protocols for treatment. However, the ophthalmologists are uniquely prepared to investigate the multifaceted impact of rare eye diseases in addressing the unmet medical need (1).

2. The burden of rarity

The designation of "rare" typically applies to diseases affecting less than 200,000 individuals within the United States. Many of these unusual ophthalmic disorders currently lack effective treatments or cures. However, advancements driven by innovative research, hold promise for unlocking solutions to some of these most challenging eye diseases. Rare ocular diseases inflict a profound detriment on patients' quality of life. Frequently it affects both the eyes (bilateral), and even if the presentation is asymmetric, it causes a significant drop in the visual acuity. Another major concern remains that the asymptomatic progression can lead to delayed diagnoses, and this can further compound the challenge.

A thorough awareness of disease pathogenesis, diagnosis, and therapy is paramount. Primary care providers recommend high-risk patients for a comprehensive ophthalmological examination and take a more active role in their care. A particular cause of concern is the limited availability of approved treatments for a significant number of these rare diseases (2). This lack of therapeutic options underscores the urgent need for further research and development efforts.

To regain a normal quality of life after a permanent vision loss, a patient requires multifaceted approach-based structure including medical care, psychological rehabilitation, and social reintegration. Patients with rare diseases frequently face a similar set of obstacles, including a lack of reliable qualitative information, delayed diagnoses, and limited access to effective treatment and specialised care. The primary concern with these diseases is that their novelty leads to misdiagnoses, under treatment, and require multiple secondary consultations and treatment trials. For these reasons, their effective management call for a two-pronged approach, viz., the healthcare system requires a robust network of specialists with expertise in these uncommon conditions and secondly sufficient resources for research initiatives for unraveling the complexities of these diseases for development of novel diagnostic tools and therapeutic interventions (3).

3. Types of ocular rare diseases

Few people are afflicted with a category of disorders known as rare diseases. Sixty-eight percent of mutations are inherited, accounting for 72% of uncommon disorders. The residual fraction is attributed to environmental causes, allergies, or illnesses (3). According to the National Institute of Health (NIH), there are about 550 uncommon eye diseases, including those that impact the retina and orbit. Cranial neural crest development plays a pivotal role in ocular health, and abnormalities in this process can manifest as a spectrum of rare eye diseases. Fate mapping studies have emerged as a powerful tool for deciphering eye development, offering crucial insights into potential pathogenic pathways. Notably, numerous rare ocular diseases have been linked to dysregulation of specific transcription factors governing cranial neural crest development. Mouse models have been successfully established for a variety of rare eye diseases affecting both the anterior and posterior segments of the eye. Some of the rare eye diseases are presented in Figure 1.

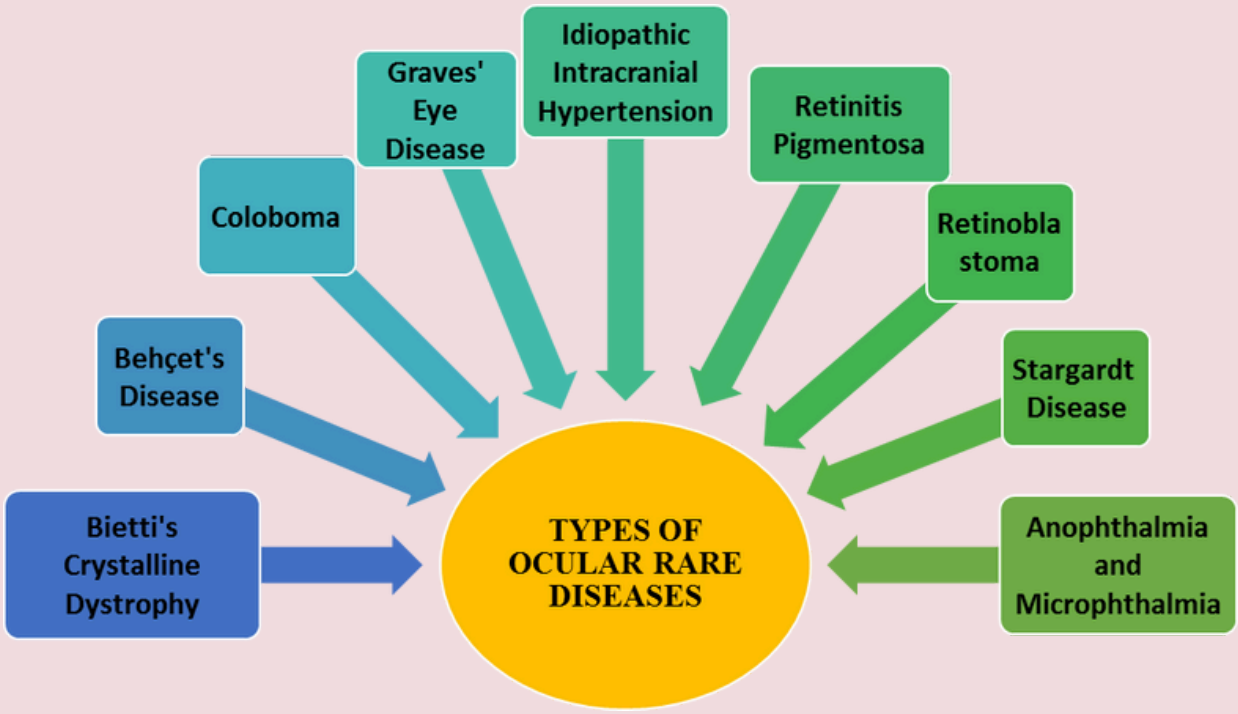

Figure 1. Types of ocular rare diseases

4. Symptoms, diagnosis and treatment of ocular rare diseases

Ocular rare diseases are those that primarily affect the eyes, are rarely seen in the general population, and frequently have little in the way of research or available treatments Depending on the exact condition, symptoms might vary greatly, however, common indications include vision loss, blurred or clouded vision, eye pain, redness, light sensitivity, and abnormalities in the appearance of the eye or surrounding tissues. Some of the ocular rare diseases with their symptoms, diagnosis and treatment are presented in Table 1.

Table 1. Symptoms, diagnosis and treatment of ocular rare diseases

S. No.	Diseases	Description	Symptoms	Diagnosis	Treatment	Ref
1.	Bietti's Crystalline Dystrophy (BCD)	Fatty acid crystals accumulate in the retina, the light sensitive layer of tissue in the back of the eye, and the cornea, the clear outer layer of the eye	Loss of vision, especially night vision, peripheral (side) vision	Dilated eye exam, genetic testing	Contact lenses, medicine, or surgery	(4)
2.	Behçet's Disease	Causes damage to blood vessels	Genital sores, red eyes, blurry vision, eye pain	Medical history	Steroids	(5)
3.	Coloboma	Occurs when a portion of the eye's tissue is absent. It could impact one or both the eyes	Loss of vision, light sensitivity, missing tissue in a portion of eye	Visual examination	early intervention, vision aids, contact lenses, spectacles, and surgery	(6)
4.	Graves' Eye Disease	The eyes expand and protrude. Also known as Graves' ophthalmopathy, or thyroid eye disease (TED), and it is brought on by Graves' illness	Dry, puffy and bulging eyes, double vision	Eye examination	Eye drops, medicine, surgery	(7)
5.	Idiopathic Intracranial Hypertension	Headaches and altered vision are brought on by elevated blood pressure surrounding the brain	Headaches, blind patches, loss of peripheral vision	Vision test, dilated eye exam, and other tests	Medication, surgery, and weight loss	(8)
6.	Retinitis Pigmentosa	Retina is affected. Slowly deteriorating retinal cells over time results in loss of vision	Loss of peripheral (side) vision and night vision	Dilated eye examination, genetic test, electroretinography	rehabilitation and low vision aids	(9)

7.	Retinoblastoma	A rare kind of eye cancer develops in the retina. It is most common in children under the age of five. One eye or both eyes may be impacted	Poor vision, eye pain, swelling, watery eyes	Dilated eye examination and ocular ultrasound	chemotherapy, phototherapy, radiation therapy, cryotherapy and ocular excision surgery enucleation	(10)
8.	Stargardt Disease	An uncommon hereditary eye condition caused by the accumulation of fatty material on the macula, the small portion of the retina required for center, crisp vision	Loss of central vision and photosensitivity	Dilated eye examination, retinal images or scans, genetic testing	Vision rehabilitation and vision aids	(11)
9.	Anophthalmia and Microphthalmia	A newborn with anophthalmia is born without one or both eyes. Microphthalmia is a condition where a baby is born with either one or both of their eyes abnormally small	These disorders have the potential to result in blindness or vision loss	Physical examination and prenatal testing	Prosthetic devices, surgery and medicine	(12)

5. Rare disease registries

Rare disease registries are a significant method for accumulating vital epidemiological information and relevant samples for clinical research, as well as for feasibility studies, particularly for clinical trial enrolment and treatment protocol development (13). By systematically collecting information on patient demographics, disease prevalence, and natural history, these registries shed light on the true scope and impact of rare diseases. This streamlined approach allows researchers to identify potential participants more efficiently and design studies with greater statistical power. Once these rare disease databases are established, a collaborative environment where all stakeholders may constantly optimise and modify them for research and clinical practice become possible. Researchers leverage these registries to formulate new hypotheses and test potential interventions. Pharmaceutical and biotechnological companies utilize the data for drug development strategies. The physicians gain access to the latest insights on the disease, which ultimately translates into improved patient care. The patients and patient advocacy groups play a vital role in shaping the content and direction of these registries, ensuring that it remains patient-centric throughout the research continuum. The European Union exemplifies the global commitment to rare disease research though its comprehensive database encompassing over 651 registries. In this vast repository, 454 are national, 77 are regional, 45 are European, 71 are worldwide, and 4 are undefined (13). It can be underscored that the rare disease registries are a powerful tool and a collective effort to advance knowledge and improve outcomes for patients with rare diseases. The list of rare eye disease registries is presented in Table 2.

Table 2. List of current rare eye disease registries (13)

S.No.	Registry	Coverage	Country
1.	Bone Cone Monochromatism- Patient Registry	International	Germany
2.	National Registry for Mycotic Keratitis	National	Germany
3.	Patient Registry for Retinal Degeneration Proretina	National	Germany
4.	Neuromyelitis Optica	National	Germany
5.	Myasthenia Gravis Registry	National	Spain
6.	Spanish Patient Registry of Hereditary Retinal Dystrophy	National	Spain
7.	Behcet's Disease Registry	National	Spain
8.	Myasthenia Gravis Registry	National	Spain
9.	Cohort of Patients with Hereditary Dystrophies of Retina	National	France
10.	Registry: An Interoperable Sustainable European Rare Eye Disease Registry	Europe	France
11.	Establishment of Children and Adolescent Cohort in Behcet's Disease in France	National	France
12.	French Cohort Creation in Retinitis Pigmentosa	National	France
13.	French Patient Registry in Chorioretinopathy, Birdshot Type	National	France
14.	French Registry of Patients Affect by Leber Amaurosis and Retinitis Pigmentosa to Assess the Clinical Trial in Gene Therapy	National	France

15.	A Cohort of Patients with Hereditary Dystrophies of Retina	National	France
16.	Curing Retinal Blindness Foundation	International	Africa
17.	Fighting Blindness Canada Patient Registry	National	Canada
18.	Retinoblastoma Registry	National	Malasia

6. Conclusion

Vision, is the preeminent sense that underpins our interaction with the world, and its impairment can have a significant impact on the quality of life and poses a public health challenge. By addressing the crucial aspects pertaining to the rare conditions, we can usher in a new era of hope for patients grappling with the sight-threatening realities of rare ocular diseases. Research efforts directed towards rare eye disorders extend far beyond isolated investigations. These studies hold immense potential for yielding insights that can be translated to benefit more prevalent ophthalmic conditions. And this assumes great importance given the high costs associated with developing treatments for rare diseases. The financial hurdles may slow down the pace of studies in rare diseases. But, the future of research in this domain brims with possibilities as we are reminded of the inspirational words of Helen Keller that “Although the world is full of suffering, it is also full of the overcoming of it”.

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In silico clinical trials for paediatric orphan diseases



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Abstract

In silico clinical trials provide an effective solution to the obstacles encountered in carrying out *in vivo* clinical trials. They have the potential to transform the approach of investigating and developing treatments for rare conditions, thereby enhancing the quality of life for individuals worldwide. To enhance existing treatment approaches, the utilization of mechanistic and data-driven modelling proves to be beneficial. These tools allow for the simulation and analysis of data obtained from *in vivo* clinical trials, as well as the categorization of subject populations. This technique has the capacity to completely transform the future of drug discovery, particularly for rare paediatric diseases.

1. Introduction

In medical research, the term "*in silico*" refers to conducting experiments on a software via computer simulation. This innovative approach is rapidly gaining attraction in the field of drug development, and it is also being explored for paediatric orphan diseases. Orphan diseases are conditions with low prevalence, the World Health Organisation (WHO) defines this as fewer than 6.5 to 10 patients per 10,000 (1). Approximately >7000 uncommon illnesses impact 25 to 30 million individuals, with roughly 4000 orphan diseases, and around 5000 patients for each orphan disease require medical attention in the United States (2). Rare disease prevalence is estimated to range from 5 to 76 per 100,000 people in non-North American and European countries. This conservative estimate puts the total number of affected individuals worldwide to about 446.2 million. There are currently 230 rare diseases being researched in the Rare Diseases Clinical Research Network (RDCRN) (3). Approximately 80% of these uncommon illnesses have a known genetic cause that involves one/more genes or chromosomal abnormalities. The rest are due to degenerative, proliferative, or teratogenic causes, allergies, or infections (bacterial or viral) (4). There were just 34 therapies available for uncommon illnesses before 1983 (2,3). As of 2021, more than 600 therapies had been approved as a result of government incentives over the previous 40 years. Despite the progress recorded, only a small percentage of patients can be treated with an approved medications. As such, between 2010 and 2015, one-third of all new drug approvals for rare diseases were granted (3). Traditional clinical trials for these diseases face significant challenges, including limited patient populations, ethical concerns, and high costs. *In silico* clinical trials offer a promising solution to these challenges, revolutionizing the way we study and develop treatments for paediatric orphan diseases.

2. Understanding the challenges

Paediatric orphan diseases present unique challenges that hinder traditional clinical trial methods. Even though public awareness has increased over the past three decades, research on rare diseases faces obstacles that include scarcity of qualified disease experts, the difficulty of securing funding for research due to limited economic impact, patient distribution across geographic regions that hinder patient recruitment for clinical trials, the requirement for specialised study designs to address the small patient cohorts, and high patient variability throughout the course of rare diseases. The rarity of these diseases makes it difficult to recruit a sufficient number of patients for meaningful clinical trials. Furthermore, because children account for 50% of patients with rare diseases, so because of ethical concerns clinical research becomes more difficult (1). It is challenging to conduct conventional randomized clinical trials (RCTs) in parallel groups due to the small patient numbers dispersed over a large geographic area. Both the inclusion of particular populations and therapies that are customized for each patient are necessary. Unfortunately, there is little to no evidence supporting the clinical trial results that are most frequently published for rare diseases. It is inappropriate to use "before/after" methodology studies without a control group or historical comparisons when evaluating drugs because these studies could be potentially biased (4). Moreover, the high costs associated with traditional trials make it financially challenging for pharmaceutical companies to invest in developing treatments for these diseases.

3. The role of *in silico* virtual clinical trials

To overcome the problems associated with a small population available for conventional clinical trials, the use of *in silico* computational models and simulations is proposed. The essential elements and biological mechanisms are first expressed in a conceptual model for *in silico* clinical trials, after which they are converted into a mathematical format (1). The limitation of small patient cohorts in rare diseases can be overcome by creating hundreds of different parameter sets *in silico*, allowing for the establishment of a large cohort of virtual subjects. Additionally, the *in silico* model is used to create a distinct paired data set of both treated and untreated virtual subjects, avoiding the difficulties that come with paediatric RCTs (4). These trials can simulate the biological processes of a disease, the effects of a drug on the body, and the likelihood of success in a virtual population (Figure 1). By leveraging data from various sources, including genomics, proteomics, and clinical studies, researchers can create sophisticated models that accurately represent the complexities of paediatric orphan diseases.

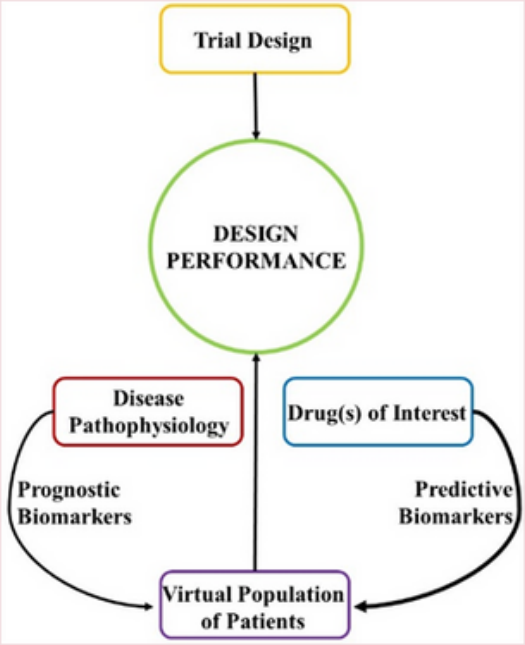

Figure 1. Essential components for modelling and simulation approach

3.1 Collection of databases

The first step to prepare any computational clinical trial model is to gather comprehensive information about a particular disease from already established clinical databases. Patient registries from a geographically defined population over an extended period, provide the highest level of evidence for epidemiological studies. These databases aim to provide data on every facet of a specific rare disease, organized into multiple primary categories (Table 1) (4). The FDA database includes 1055 medications list and provides information on the indications related to orphan drug and chemical structures (3).

Table 1. Data sources for rare diseases (3)

Dataset	Use	Reference
FDA Orphan Drug Designations and Approvals	Drugs associated with rare diseases	www.accessdata.fda.gov/scripts/opdlisting/oopd/
MalaCards	The human disease database	www.malacards.org/
Pharos	Targets associated with diseases	https://pharos.nih.gov/
ClinVar	Gene variations and associated conditions	www.ncbi.nlm.nih.gov/clinvar/
OMIM	Association between human genes and genetic disorders	https://omim.org/
GeneCards	Genes information	www.genecards.org
NORD	Signs and symptoms of rare diseases	https://rarediseases.org/
Rare Disease InfoHub	Symptoms of rare diseases (including experts and funding opportunities)	https://rarediseases.oscar.ncsu.edu/
Genetic and Rare Diseases Information Center	Synonyms, summary, and symptoms for rare diseases	https://rarediseases.info. nih.gov/

3.2 Analysis of databases

3.2.1 Prognostic biomarkers

A biomarker is considered prognostic when its values at the beginning or its changes over time are linked to a clinical outcome that is unrelated to the treatment. Prognostic biomarkers are linked with a specific favourable or unfavourable evolution of the disease. Its correlation with the clinical endpoint needs to be consistently shown in separate investigations, ideally spanning a variety of clinical scenarios, for it to be considered validated. Contrary to popular opinion, heterogeneity is typically more advantageous from a statistical standpoint than disadvantageous. Prognostic biomarkers may only need to be initially identified and statistically validated through retrospective studies; however, prospective studies may be required to confirm the clinical utility of the biomarker (4).

3.2.2 Predictive biomarkers

A biomarker is considered predictive when it is shown that its initial value or subsequent changes can accurately predict the effectiveness or harmful effects of a treatment, as judged by a certain clinical outcome. RCT data involving patients with high and low biomarker levels is necessary for the statistical identification of predictive markers. To find potential predictive biomarkers and validate them sufficiently for inclusion in clinical practice and trial designs, retrospective analyses might be adequate. However, for conclusive evidence, prospective clinical trials might still be required (4).

3.2.3 Analysis of potential treatments

Various methodologies have been proposed to assess the impacts of interventions in observational studies. The primary goal of all these techniques is to address confounding, or potential bias brought on by the nonrandomized treatment assignment (5). The most popular techniques are:

i. Observational study designs: Case-crossover, Case time-control, Historical controls, Treatment candidates, Comparisons of treatments for the same indication
ii. Data-analytical techniques: Asymmetric stratification, Propensity score adjustment, Two-stage least squares, Common multivariable statistical techniques, Instrumental variables, Simultaneous equations, Stratification and matching on specific covariates

3.3 Disease/drug effect modelling

Several models of diseases have been published in the literature thus far. Their mathematical formulation relies on partial differential equations (PDEs) and/or ordinary differential equations (ODEs), which serve as the foundation for these models. These models are often used to simulate the progression of biomarkers during the course of disease development. Pharmacokinetic-pharmacodynamic relationships serve as the foundation for treatment effect modelling most of the time, and models on this subject are already available. These models are particularly helpful in anticipating biomarker changes following a modification in the dosage of a treatment (5).

4. Strategy for simulation

Conducting simulated clinical trials of a drug in virtual populations allows for direct observation of the treatment's effect impact on the diseased population. Any simulation model for a given therapeutic technique is categorized into one of these sub-models (6):

- Patient outcomes are predicted by the input-output (IO) sub-model. It includes the pharmacokinetic/pharmacaodynamic (PK/PD) characteristics of the medicine, as well as a pathophysiology model of the condition, if exists. In order to accurately replicate drug concentrations, biomarkers of therapeutic or toxicological response, or the occurrence of a clinical outcome or adverse event, it is necessary to determine the parameters and structure of the model using the data obtained from clinical research.

- Using already-existing patient databases, the covariate distribution sub-model explains patient features.

- The execution sub-model describes the features of experimental designs and deviations from protocol that are related to patients or researchers.

Assessment of simulation results: Assessment is carried out in the same population following drug or placebo exposure. This method allows for the exploration of a wide range of scenarios pertaining to RCT designs, drug dosages, drug associations, patient selection, exposure duration, etc. The following are the primary steps:

1. Patient samples for in silico RCTs that are chosen at random from the "validated" virtual population.
2. Optimizing and limiting the number of simulations by using a pre-established simulation strategy.
3. Applying the same particular statistical analysis to every set of simulated RCT outcomes.

Analysis of simulation results: The final analysis should identify the most relevant medications (using multiple-criteria decision analysis techniques) and experimental designs for phase III RCT evaluation.
The majority of this analysis would be descriptive. The number of times a significant result is produced in each trial should be used to rank each scenario, including trial design and "rare disease-drug" pairs. Trial length and the accuracy of treatment effect estimates are considered in this final hierarchy (6).

5. Case study (1)

Mutations in Neurofibromatosis Type 1 (NF1) are linked to congenital pseudoarthrosis of the tibia (CPT). A gradual bending of the tibia that leads to spontaneous fractures in the distal portion of the tibia is the hallmark of the unusual condition known as CPT. Pseudoarthrosis is usually caused by insufficient bone regeneration and is treated with either internal or external fixation or by physically excising the abnormal bone tissue. Recombinant human bone morphogenetic protein, or rhBMP-2 or rhBMP-7, is used in clinical practice these days to improve surgical outcome. Nonetheless, there is ongoing controversy regarding the efficacy of BMP therapies, and the United States Food and Drug Administration (U.S. FDA) has cautioned against using BMP in patients who are skeletally immature. Researchers concentrated on the eight parameters that were identified in the literature as having a part in the inadequate fracture-healing outcome in CPT. In order to investigate the impact of the NF1 mutation on bone-fracture repair, the parameter values of the variables representing the abnormal cellular activity of NF1-haplodeficient and NF1-null cells were varied throughout a wide range in the computational model.

Following is the list of selected eight parameters (normal and NFI range respectively):

- Invasion time fibroblasts (3, 0-50)
- Fibroblastic proliferation (0.1, 0.1-10)
- Fibroblastic differentiation (0.01, 0.01-1)
- Osteogenic differentiation (20, 0-20)
- Endochondral ossification (1000, 0-1000)
- Cartilage formation (0.2, 0-0.2)
- Fibrous tissue formation (0.2, 0.2-10)
- Angiogenic growth factor production (10^3, 10^3- 10^5)

Method: The *in silico* clinical trial comprised of 200 virtual individuals, where the healing process was simulated both with and without BMP treatment. The JMP "Design of Experiments" (DOE) tool was used to create the 200 virtual subjects. By primarily modifying the parameter values of the eight components in one direction relative to the normal case, the parameter space was identified, biasing the DOE design toward a CPT phenotype. One generic osteochondrogenic growth factor (gbc) was used to model BMP treatment. This model allows for the simulation of the effects of multiple growth factors that are released from the BMP sponge as a clinical treatment and are present in the fracture callus.

Observation: The complication index (CI) mathematically analyses the degree of severity of CPT by integrating the three most prevalent symptoms a non-union, haematoma, and presence of fibroblasts in a linear form. When a combination of criteria results in decreased CI value, it suggests a low level of CPT severity, implying that the fracture healing process is progressing reasonably smoothly. On the other hand, a combination of criteria that generates a high confidence interval (CI) implies considerably reduced fracture healing and is similar to the CPT phenotype.

Results: Using an arbitrary cut-off of CI value of 0.5, four distinct groups were clustered comprising the virtual subjects:

1. Adverse responders (having a high CI when treated, but a low CI when left untreated)
2. Non-responders, both with and without treatment (high CI)
3. Asymptomatic (low CI, both with and without treatment)
4. Responders (lower CI after treatment and higher CI when left untreated)

In order to identify highly correlated (redundant) attributes, researchers first computed the Spearman correlation matrix of the dataset, the outcomes indicated the lack of association between the NF1 parameters. The correlation between the CI value and the bone tissue fraction was as anticipated to be negative and positive with the fibrous tissue fraction. To conduct a more thorough analysis of the CI data, they examined the various elements that make up the CI value, such as the quantity of fibrous tissue remaining after 49 days. There was a fascinating difference in the amount of fibrous tissue for each subject class at day 49 post-treatment, with the responding subjects having substantially less fibrous tissue than the other subject classes. Every virtual patient was made to experience both no treatment and a treatment with bone morphogenetic protein (BMP). It was demonstrated that, although very subject-specific, BMP treatment significantly reduces the degree of severity of CPT (1).

6. Regulatory requirement for *in silico* models

The regulatory authorities around the world share the need for regulatory guidance for in *silico* model validation. When the modelling and simulation data are merely regarded to have a descriptive role and the crucial information for the question being answered comes from other sources, the regulatory impact is deemed to be minimal. Nonetheless, the regulatory impact is judged to be substantial when modelling results serve as the primary source of evidence to address the important question by substituting data normally generated in a clinical trial (7). Two global regulatory bodies that embrace and promote the use of modelling and simulation in the regulatory process are the European Medicines Agency (EMA) and the U.S. Food and Drug Administration. Further efforts are needed from other regulatory bodies across the globe to integrate this new evidence into the regulatory framework (8).

7. Conclusion

In silico clinical trials hold immense promise for the future of drug development, particularly for paediatric orphan diseases. Today, researchers can successfully conduct an in silico clinical trial, and analyse the outputs. The next logical step would be to compare the simulated cohort with the real patient-specific parameter distributions. As computational models become more sophisticated and data sources become more abundant, the accuracy and reliability of in silico trials will continue to improve. This approach has the potential to revolutionize the way we develop treatments for rare diseases. To improve current treatment strategies, mechanistic and data-driven modelling are helpful tools for simulating and mining data from in silico clinical trials and stratifying subject populations.

This kind of robust modelling can also be used to identify biomarkers, optimize dosage, or determine how long to propose an intervention. Validating in silico clinical trials for rare diseases and identifying any flaws in the computational model in the event of differences between the predicted and measured in vivo outcomes would be made possible by real patients participating in in vivo experiments.

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Rare sclerosis unmasked: Insights into orphan drugs for amyotrophic lateral sclerosis


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Abstract
Orphan drugs are essential for the treatment of rare diseases, which impacts 3-6% of global population. These conditions are often overlooked by major pharmaceutical companies due to the limited commercial viability, leading to WHO (World Health Organisation) to term them as 'neglected'. This article explores various types of rare sclerosis and focuses on Amyotrophic lateral sclerosis (ALS), its current treatment options and approved orphan drugs. Various types of rare sclerosis include Balo's concentric sclerosis (BCS), Schilder's disease, Tumefactive multiple sclerosis, multiple sclerosis (MS) and Amyotrophic lateral sclerosis (ALS). All these types affect central nervous system (CNS) with varying pathophysiology and symptoms. While no specific orphan drugs exist for these (Balo's concentric sclerosis, Schilder's disease, Tumefactive multiple sclerosis) types, symptoms are managed by corticosteroids, interferons and immunosuppressants. Multiple sclerosis (MS) has disease modifying therapies (DMT) available which includes Beta interferon and Glatiramer acetate. ALS is a progressive neurodegenerative disease that affects motor neurons. Its pathophysiology involves glutamate excitotoxicity, gene mutations, oxidative stress, and neuroinflammation. Current treatments include Riluzole and Edaravone; the combination of Sodium Phenylbutyrate and Taurursodiol was discontinued due to safety concerns. Novel approaches like small molecules, gene therapy, and stem cell treatments are under evaluation. Some drugs were granted Orphan designations for ALS, such as Riluzole (EXSERVAN), Edaravone (RADICSAVA), and Tofersen (QALSODY), while Lenzumestrocel is under clinical evaluation. Despite their small market share, orphan drugs are crucial for addressing rare diseases. Enhancing their identification, diagnosis, prevention, and treatment will result in improved healthcare outcomes for affected individuals.

1. Introduction

In the vast landscape of pharmaceuticals, there exists a remarkable class of medications for their profound impact on patients grappling with some of the rarest and most debilitating diseases known to humanity. These medications, categorized as rare and orphan drugs, serve as beacon of hope for patients and families facing conditions typically neglected during traditional drug development efforts.

Rare disease, as the name suggests, affects only a small fraction of global population around 3-6%. Due to absence of a universal definition, varying criteria have emerged to identify a rare disease across countries (1). In response to their unmet medical and social needs, the concept of orphan drugs emerged. Orphan drugs are designated to diagnose, prevent or treat rare diseases such as acute intermittent porphyria, myasthenia gravis and merkel cell carcinoma (2, 3). The WHO refers to these diseases as “neglected” because they are overlooked by major pharmaceutical companies due to limited commercial viability.

This article delves into the various types of rare sclerosis and highlighting the details on Amyotrophic lateral sclerosis (AML), along with current treatment options and approved orphan drugs.

2. Rare types of sclerosis

There are various types of rare sclerosis that includes Balo concentric sclerosis (BCS), Schilder disease, Tumefactive multiple sclerosis alongside more prevalent ones like Multiple sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) (4) as mentioned in the Table 1. All the types of sclerosis affect the CNS with varying pathophysiology and neurological involvement.

Table 1. Types of rare sclerosis (5–8)

Type	Description	Symptoms
Balo’s concentric sclerosis (BCS)	Histological variant with characterized by concentric layers of demyelination (onion ring) in the brain	Headache, weakness, seizures, sensory disturbances and cognitive impairment
Schilder's sclerosis	Diffuse cerebral sclerosis with extensive demyelinating of the cerebral brain with one-two symmetrical bilateral plaque	Spasticity, seizures, visual disturbances and cognitive decline
Tumefactive multiple sclerosis	Rare form of multiple sclerosis which has emergence of large lesions (tumour-like) demyelination in brain	Symptoms may mimic other types of MS but can also cause seizures and changes in mental status
Multiple sclerosis (MS)	Characterized by chronic inflammation and demyelinating of myelin sheath which results in neuron loss in the brain and spinal cord	Vision impairment, numbness, weakness, tremor, constipation, bladder and bowel incontinence and cognitive dysfunction

Currently, there are no orphan drugs available for these types of sclerosis. However, management of their symptoms can be achieved using corticosteroids, interferons and immunosuppressant drugs (8,9).Meanwhile, therapies such Beta interferon (Avonex, Betaseron and Rebif) and Glatiramer acetate (Copaxone) are considered as disease-modifying therapies currently used in the treatment of Multiple sclerosis (MS) (10,11).

3. Amyotrophic lateral sclerosis (ALS), current treatment and approved orphan drugs

It is a rare progressive neurodegenerative disease that affects neurons in the spinal cord and brain (12). Also, known as Lou Gehrig's disease. 'Amyotrophy' refers to muscle fibres atrophy and 'Lateral sclerosis' refers to hardening of motor neurons. It degenerates motor neurons that controls their voluntary muscle control while sensory functions are typically preserved (13). The rate of disease progression varies depending on onset age and site. Typical symptoms include difficulty in speech and swallowing, atrophy and eventual respiratory failure (14).

According to Lu Xu *et al.* in 2019, the worldwide prevalence and incidence were 4.42 and 1.59 per 1, 00, 000 person/year respectively (15). Whereas, worldwide prevalence is between range of 3.4- 12.3 per 10,00,00 persons. Overall, there is slightly higher incidence of male prevalence than female (M: F~ 3:2.4) (16).

The exact pathophysiology that leads to neuro-degeneration of ALS is still unknown. However, various neurodegenerative diseases are mediated through complex interrelated molecular and genetic pathways. Below mentioned pathways as shown in Figure no.1 are implicated in pathophysiology of ALS (17, 18).

3.1 Glutamate excitotoxicity:

The dysfunction of the astrocytic excitatory amino acid transporter 2 (EAAT2) mediates reduction in the uptake glutamate in the synaptic cleft. This leads to the induction glutamate excitotoxicity through activation of Ca 2++ -dependent enzymatic pathways, further, impairing glutamate clearance and ultimately contributing to neurodegeneration.

3.2 Mutations

in c9orf72, TDP-43 and FUS leads to defects in protein degradation pathways leading to dysregulation in RNA metabolism and impaired protein synthesis which causes translation abnormalities and formation intracellular neuronal aggregate.

3.3 SOD-1 Mutation:

Superoxide dismuates-1 (SOD-1) gene mutation results in Neurofilaments, dysfunctional mitochondria and disruption of axonal transportation due to oxidative stress and leads to intracellular aggregates.

3.4 Neuroinflammation:

Microglia activation resulted by secretion of cytokines which leads to inflammation and neurotoxicity.

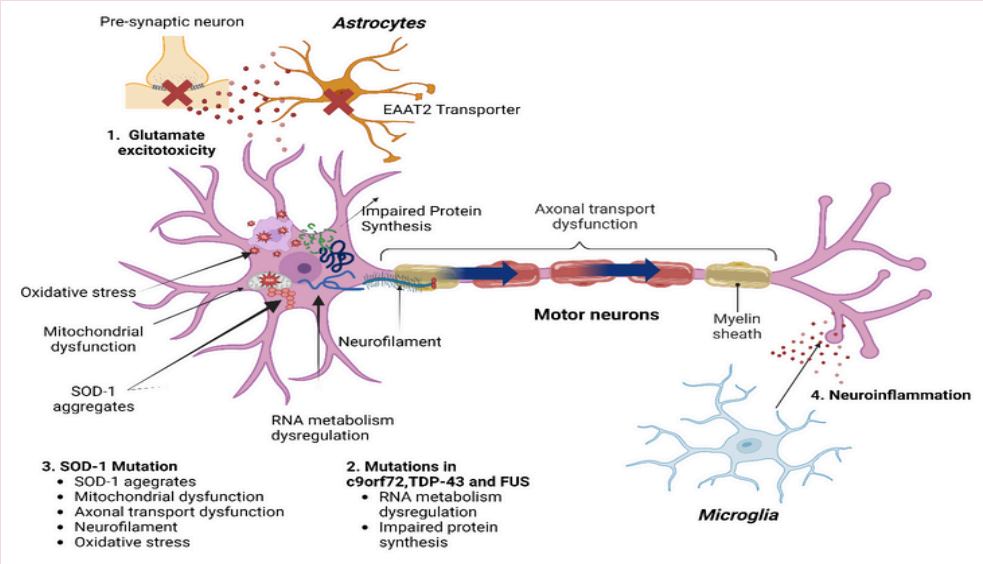

Figure 1. Pathophysiology of Amyotrophic Lateral Sclerosis (ALS) (Created by Biorender)

The current available treatment options help in the management of symptomic relief and slows the progression of the disease. Below mentioned drugs are majorly used in ALS treatment.

- Riluzole was approved initially approved by FDA in 1995 for oral use as the treatment of ALS. Its exact mechanism is unknown, but it acts on glutamate as antagonist. This slows the progression of disease by inhibiting glutamate release (excitotoxicity) in presynaptic neuron (19).
- Edaravone was approved by FDA in 2017. It is available in injectable form as oral suspension powder. It is known inhibits lipid peroxidation that eliminates radicals such as hydroxyl, peroxynitrite, peroxyl hydrogen peroxide that acts as reactive oxygen species (ROS). Hereby, protecting the neurons in the spinal cord and brain by reduction of oxidative stress and lesser neurodegeneration
- Combination of Sodium Phenyl butyrate and Taurursodiol promotes the inhibition of neuronal death by reduction in Endoplasmic reticulum (ER) stress and mitochondrial dysfunction (19). However, post Phase 3 Phoenix III trail Relyvrio was voluntarily discontinue from the market due to safety concerns (10).

Many drugs of different therapeutic categories such as anti-inflammatory, anti-excitotoxicity and anti-aggregation agents are being evaluated for the treatment of ALS. Novel approaches such as small molecules, gene therapy and stem cell are in trials for its assessment as new treatment options (20). Other types of palliative cares such as counselling and rehabilitating therapy that are symptom dependent are needed to improve the quality of life.

The above-mentioned drugs after various clinical trials and years later were approved to treat ALS as designated orphan drugs by different regulatory agencies across the world. The below table 2 represents the approved orphan drugs with product information and mechanism of action (MOA**).**

Table 2. Approved orphan drugs for Amyotrophic Lateral Sclerosis (ALS)

Molecule	Orphan Indication year	Innovator & Brand Name	Dosage & Strength	MOA
Riluzole	2019	Aquestive Therapeutics (EXSERVAN)	Film- 50 mg	Inhibits the glutamate, Inactivates sodium channels (voltage dependent), G-protein activation for transduction process.
Edaravone	2024	Mitsubishi Tanabe Pharma Corp (RADICSAVA)	Oral Suspension 105 mg/5 ml	Inhibits lipid peroxidation
Tofersen	2023	Biogen MA Inc (QALSODY)	Injection 100 mg/15 ml	Targets SOD1 mRNA to lower the SOD1 protein synthesis

The clinical trial ALSUMMIT (NCT04745299) is an on-going Phase III trial conducted at multiple centres and was initiated in 2021. This study design is random, double blind conducted in parallel group with sham procedure-control. It aims to assess the safety and efficacy (long-term) of the Lenzumestrocel- Neuronata-R® Injection to treat ALS patients upto 36 months. The trial involves 115 subjects and is expected to be completed by 2026. Lenzumestrocel has received conditional approval in Korea as orphan cell therapy by its regulatory authority (MFDS) for ALS (21).

4. Conclusion

In conclusion, despite representing a small portion of the pharmaceutical market there is need to emphasis upon understanding and addressing multifaceted nature of rare diseases that includes identification, diagnosis, prevention and development of orphan drugs (22). The encompassing factors includes complex biology, low prevalence rate, expertise in the area, methods and instruments used, developing the tailored drugs for rare diseases (23). By focusing on these areas, we can serve individuals affected by rare diseases and improve their overall healthcare outcome in an effective manner.

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Aplastic anemia: Insights and updates

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Abstract
Aplastic anemia (AA) is a rare condition characterised by reduction in production of blood cells due to damaged bone marrow function. In AA, there is autoimmune response towards the bone marrow cells that results in its impairment. AA pathophysiology revolves around upregulation of T cells and pro-inflammatory and inflammatory cytokines. AA has multiple causes and pathogenic factors, and all lead to destruction of hematopoietic stem cells. Many molecular proteins and cascades are associated with pathological advancement in AA. Diagnosis of AA is also challenging. AA is generally diagnosed by blood cell count and haemoglobin determination. However, for differential diagnosis various protein markers for peripheral blood can be utilised. Therapeutic considerations for AA mainly include haematopoietic stem cell transplant and immunosuppressants. However, nowadays, may novel therapies as well as new regimens are discovered. Such novel approaches prove promising for therapeutic advancement and possible cure for AA. Extensive studies through collaborative efforts in this area can lead to better therapies for mitigation of AA.

1. Introduction
Aplastic anemia (AA) is a rare condition in which there is unwanted immune response towards haematopoietic cells that result in impaired bone marrow function and less production of peripheral blood cells (1,2). About 32.9% people were found to suffer from AA worldwide up to 2010. Children (up to 5 years), infants and pregnant females were more susceptible to AA. It is generally observed that risk of AA was more in female than male population. It was also observed that AA risk increased with increasing age in geriatric people (3). Additionally, it was seen that AA prevalence was high in Asian countries as compared to western countries like America. Contrary to previous findings, in an epidemiological study it was observed that prevalence of AA was higher in male than in female. Out of 1324 patients, 997 patients of AA were male whereas 327 were female patients. Cases of severe and very severe AA were comparatively higher than non-serious form of the disorder. It was also found that majority of patients belonged to low socioeconomic status (4). T-cells are abnormally activated which result in decreased hematopoietic stem cells and progenitor cells (5). Clinical manifestations of AA include fatigue, dyspnoea, bruising, gingival bleeding, heavy menstruation, fever and headache (1).

1.1 Pathogenesis

In patients of AA, it is observed that expression of T-box transcription factor TBX21 (T-bet) is elevated. Increase in T-bet further leads to imbalance of type-1 and type 2 helper T cells (Th1 and Th2). This consequently leads to upregulation of proinflammatory cytokines that include Interleukin-2 (IL-2), tumour necrosis factor-α (TNF-α), and Interferon-γ (IFN-γ). Furthermore, these processes collectively lead to negative regulation of haematopoiesis and Fas mediated apoptosis of haemopoietic stem cells. Additionally, regulatory T cells (Tregs) are also impaired in AA. These also leads to increase in T helper 17 cells (Th17) and upregulation of retinoic acid receptor related orphan receptor gamma (RORγt) and inflammatory cytokines. Other than this, mutations in Janus-Kinase (JAK)- signal transducer and activation of transcription (STAT) and mitogen activated protein kinase (MAPK) signalling cascades also lead to clonality of CD8+ T cells. Production of cytotoxic T cells is affected due to the presence of defective NK cells (5). It was reported in a study that there was an increase in levels of IL-2, IL-6, IL-8, TNF-α and INF-γ in either peripheral blood or serum of AA patients. Upon administration of mesenchymal stem cells, it was found that levels of TNF-α, IFN-γ and IL-2 were reduced, whereas increased levels of transforming growth factor β (TGF-β) were observed. In addition, it was established that CX3C motif chemokine ligand (CX3CL1) and CX3C motif chemokine receptor 1 (CX3CR1) were implicated in pathogenesis of AA. Interaction of these stimulates release of T cells in bone marrow. Increased levels of CX3CL1 were seen in patients of AA. Interestingly, another interleukin IL-21 was also found to be involved in pathophysiology of AA. IL-21 not only suppresses Tregs, but also increases IL-17. Furthermore, it alters the expression of Forkhead box protein 3 gene (FOXP3) (6) (**Figure 1**).

1.2 Diagnosis

Complete blood count, bone marrow biopsy or aspiration, reticulocyte count and leukocyte differential count are commonly used techniques for AA diagnosis (1). Differential diagnosis in AA is quite challenging. However, there are some diagnostic markers associated with AA that include glycosylphosphatidylinositol anchored protein deficient blood cells and HLA class I allele lacking leukocytes. It is also observed that expression of T-cell immunoglobulin and mucin domain 3 (TIM3) is decreased in AA patients. TIM3 marker suggests the maturation of natural killer cells. However, the decreased expression of TIM3 indicate defect in these cells (5). Most common characteristics for diagnosis of AA include presence of two lineage cytopenia. Other hallmarks include haemoglobin less than 10 g/dL, platelet count less than 50 X 109/L and neutrophil count less than 1.5 X 109/L. Severe AA is characterised by neutrophil count lower than 0.5 X 109/L, platelet count lower than 20 X 109/L, reticulocyte less than 20 X 109/L and reduction in normal cellularity of bone marrow to 25% (7) (**Figure 1**).

1.3 Current therapeutics used for AA

Generally, conventional therapeutic strategies in AA involve use of immunosuppressive therapies, blood transfusion and stem cell transplantation (2,5). Transfusion therapy is preferred for patients having multiple comorbidities (5). Anti-thymocyte immunoglobulin (ATG) along with cyclosporine are amongst the most common treatment strategies for AA(2). Haemopoietic stem cell transplant (HSCT) is the foremost approach as transplant therapy. Subsequently HSCT is followed by administration of immunosuppressants like cyclosporine (2). However, HSCT poses a risk for ABO mismatch. In these cases, treatment options include transfusion of red cell units that are compatible to the donor (8). Some other complications can also occur. Minor ABO mismatch also requires transfusion of donor compatible red cell units. Sometimes it is observed that residual plasma cells of recipient cause immune tolerance. In this case, transfusion is preferred. Other transplant options include bone marrow transplant from sibling matched donor (1).

Additionally, administration of rituximab (anti-B cell), donor lymphocyte infusion, erythropoietin, TPO mimetics, Syk inhibitor, intravenous immunoglobulin, daratumumab (anti-plasma cell), bortezomib (anti plasma cell) might be considered. Another complication is development of new autoantibodies along with immune tolerance and mixed chimerism. For this, treatment options include administration of intravenous immunoglobulin, corticosteroids, rituximab, erythropoietin, Sky inhibitor, anti-plasma cell therapy, immunosuppressants, anti-complement or splenectomy (8).

Other than these, thrombopoietin receptor agonists can also be used. These include compounds like eltrombopag, romiplostim, avatrombopag and hetrombopag. These conventionally increase platelet count, however in AA, these drugs stimulate residual hematopoietic stem cells and enhances haematopoiesis (5). Amongst these agents, eltrombopag is widely used in AA.

Androgens are another choice of drug for treatment of AA. These are able to upregulate erythropoietin secretion and haematopoiesis. Additionally, it is observed that there are mutations in telomerase and its RNA component (5). In these cases, androgens also increase activity of telomerase. Androgens and androgen related agents are used which involve testosterone undecanoate, danazol and stanozolol (5,9).

Rapamycin is another agent implicated for treatment of AA. It inhibits mammalian target of rapamycin (mTOR) which has a rather significant role in mitochondrial metabolism of T cells. It also inhibits IL-2 release stimulated by activated T-cells. Alemtuzumab is also used for treatment of AA. It induces depletion of lymphocytes by targeting CD52 and ultimately leads to regulatory phenotype T cells recovery (5). Granulocyte colony stimulating factor (G-CSF) is also used as therapy. It is responsible for expansion of haematopoietic stem cells, inhibits apoptosis, promote differentiation of neutrophils. Some other immunosuppressants like cyclophosphamide, levamisole and mycophenolate mofetil are also used for AA therapy (5) **(Figure 1).**

2. Advancements in AA therapies

Nowadays, unconventional and neoteric approaches with respect to AA treatment are being developed.Similar to HSCT, umbilical cord blood transplantation is one of the unconventional approaches. Initially, cyclosporine was commonly used post-surgery. However, new regiments including agents like melphalan and fludarabine are also used these days (2). There is impairment of telomerase RNA component (TERC) in case of AA. TERC is involved in extension and maintenance of telomeres. TERC haploinsufficiency affects length of the telomer and results in conditions like AA. A new therapeutic strategy, cell reprogramming allows to reverse differentiation of cells and transforms cell into pluripotent stem cells with more ability. Furthermore, programming can affect length of telomer and can extend it. TERC cell reprogramming is thus a promising strategy for therapy of AA. Cells like mesenchymal stem cells and induced pluripotent stem cells (iPSC) can be used for this purpose (10).

In a phase II clinical trial for AA, it was found that avatrombopag along with immunosuppressive therapy in refractory AA patients was effective. The trial was conducted in two cohort groups. The first group consisted of severe AA patients who have not yet received any therapy. Another group consisted of severe AA patients who had refractory or relapse condition after therapy. First group received anti-thymocyte globulin and cyclosporine along with avatrombopag for 180 days. The other group received avatrombopag with or without any additional therapy (11). Another trial involved determination of efficacy of romiplostim in refractory AA patients. Romiplostim is a fusion protein that stimulates thrombopoietin receptor and consequently activates transcriptional pathways that ultimately stimulate hematopoietic cells, megakaryocytes and progenitor cells. Initially the study was conducted for 53 weeks, however

efficacy was not adequate, hence the study was extended up to 3.5 years and closely observed patients who took romiplostim in their regimen. This long-term therapy proved to be effective and relatively safe for therapy of AA (12). Another study evaluated the prophylactic effect of ruxolitinib prior to allogenic stem cell transplantation in 35 patients. Following the transplantation there is a prominent risk of graft versus host disease. To eliminate this possibility, ruxolitinib was administered to reduce the risk of this occurrence. Administration of ruxolitinib exhibited less risk of graft versus host disease, lower infections, restoration of Tregs and CD4+ cells. This shows that ruxolitinib is effective in such conditions (13) (Figure 1).

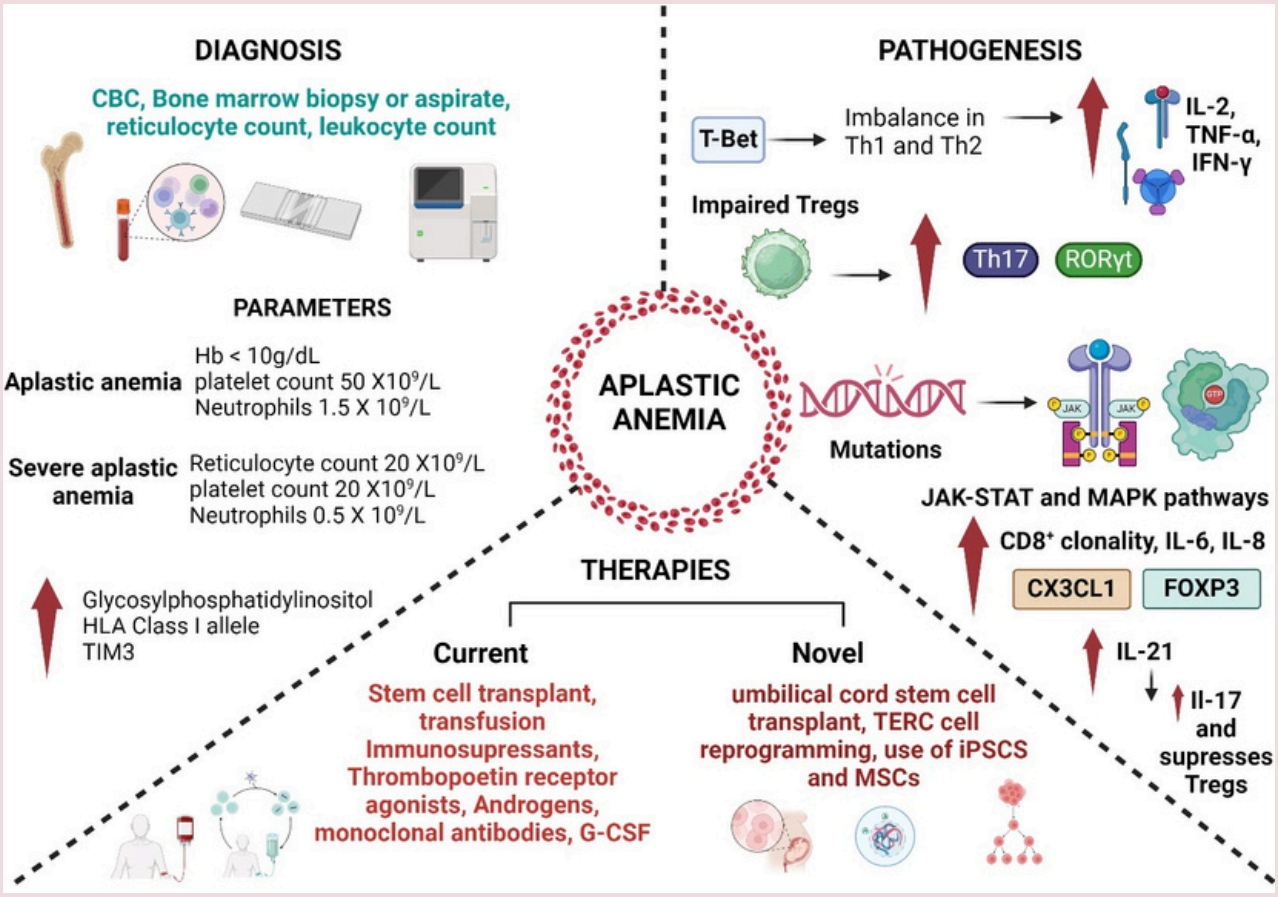

Figure 1. Diagnosis, pathogenesis and therapies for aplastic anemia

3. Challenges and opportunities in AA research

AA is a rare disease and hence, research in this area is scarce. Research should be extensively promoted in this area, as there are many challenges for therapeutic intervention for AA. Stem cell transplantation is the foremost treatment strategy in AA. However, it poses a challenge to find a donor that matches the patient in a time bound manner. To overcome this haploidentical stem cell transplantation technique can be used. This technique has been reported to lower the prevalence of graft failure and occurrence of graft versus host disease. Such techniques can be explored more, and further extensive research should be carried out in these areas to overcome these types of challenges in therapy of AA (14). Another major challenge for mitigation of the disease is the lack of specific treatment for AA patients. This might lead to less chances of survival of the patients. More resources are required to design a specific regimen for AA therapy.

Availability of such resources can prove to be helpful for treatment of AA. Also, it was observed that mortality for severe AA cases also involves factors like presence of other comorbidities like infection. Haemorrhage is also one of the leading causes of death in severe AA. These issues can be minimised through selection of suitable therapeutic alternatives with respect to the condition of patient (15). Government organisations can provide aid for conducting these studies that will probably help in providing remission to AA patients. Aplastic anemia and myelodysplastic disease syndromes (MDS) International foundation is a USA based foundation that promotes research as well as provides primary care to AA patients (16). In India, DKMS-BMST foundation is a non-profit organisation that promotes research and primary care for disorders like AA, blood cancer and thalassemia (17). Such non-profit organisations might help promote and advance research in these rare areas and hence support to such entities should be encouraged. Industry-academia-government collaboration should be highly encouraged to promote research and development of treatment modalities and algorithms for the treatment of AA.

4. Conclusion

AA is a rare blood related disorder in which there is less production of blood cells. It usually occurs through dysfunction in bone marrow due to untoward auto immune response. Diagnosis and therapy in AA pose quite a challenge. However, differential diagnosis of AA is possible through various markers in peripheral blood. It is observed that therapies for AA majorly include stem cell transplant and administration of immunosuppressants. Moreover, nowadays novel techniques like TERC cell reprogramming and other transplants are being developed for clinical use. More emphasis on these novel procedures can lead to successful mitigation of AA.

5. **Acknowledgment**

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Unveiling the hidden epidemic: Navigating orphan and rare diseases in healthcare



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1 . Introduction

Orphan and rare diseases, often overlooked, impact a small proportion of the population, presenting unique challenges in diagnosis, treatment, and support. According to the Orphan Drug Act of 1983 in the United States of America, rare diseases impact fewer than 200,000 persons on average, but orphan diseases, according to the European Union (EU), affect fewer than 5 in 10,000 people (1). These illnesses cover a wide range, including genetic problems, some tumours, and autoimmune diseases. It is crucial to treat orphan and rare diseases for the benefit of both society at large and the afflicted individuals directly (2). Despite being uncommon, millions of people worldwide are impacted by orphan and rare diseases, which have a high morbidity and mortality rate. Due to their complex nature, many diseases require specialised attention and disproportionately affect vulnerable communities, exacerbating health inequities. Ignoring these problems hinders not only the quality of life of individuals and their families but also the progress of science and medicine (3). Orphan and rare diseases are a broad category of illnesses that are characterised by their rarity and often complex aetiology. Treatment and diagnosis of these conditions can be complex due to the way they impact several organ systems and create a wide range of symptoms. Orphan and rare diseases, the exact aetiology of which is yet unknown, are caused by a variety of reasons, including genetic alterations, environmental factors, and autoimmune dysregulation (4). Here, we look at a few distinct types of rare and orphan diseases (depicted in figure 1) and discuss their underlying causes:

1.1 Genetic disorders:

Duchenne muscular dystrophy, cystic fibrosis, and Huntington's disease are a few examples.

Cause: It is genetic mutations passed down from one or both parents, which lead to aberrant development or improper activity of certain genes or gene products. By interfering with vital biological processes, these mutations can result in a wide range of symptoms and outcomes (5).

1.2 Metabolic disorders:

PKU, Fabry disease, and Gaucher disease are a few instances.

Cause: Dysfunctions or imbalances in the metabolic pathways or enzymes that cause the breakdown or processing of certain substances, such as lipids, amino acids, or carbohydrates. The substances in question have the potential to build up within the body, resulting in harmful effects and tissue damage (6).

1.3 Autoimmune disorders:

Systemic lupus erythematosus (SLE), myasthenia gravis, and Sjögren's syndrome.

Cause: Dysregulation of the immune system results in the production of autoantibodies which attack and target healthy tissues and organs. The aetiology of autoimmune diseases is multifaceted and may involve immune system dysfunction, environmental triggers, and genetic susceptibilities (7).

1.4 Neurological disorders:

ALS, narcolepsy, and Rett syndrome are a few manifestations.

Cause: There are several factors that can lead to neurological issues, including imbalances in neurotransmitters, aberrant brain development, genetic mutations, and neurodegeneration.

Such circumstances often involve complex interactions involving genetic and environmental factors (8).

1.5 Rare cancers:

Cholangiocarcinoma, pancreatic neuroendocrine tumours, and mesothelioma are a few instances.

Cause: Unusual cancers tend to be more common or are brought on by specific genetic mutations or environmental exposures, despite the fact that smoking, radiation exposure, genetic predisposition, and other known risk factors are linked to a high risk of cancer. To enhance outcomes and develop targeted treatments, it is imperative to understand the underlying causes of rare malignancies (9).

1.6 Infectious diseases:

Lassa fever, Ebola virus sickness, and Creutzfeldt-Jakob disease are among them.

Cause: Infections with uncommon pathogens such prions, certain viruses, or bacteria can result in rare infectious illnesses. Such infections could only take place in specific locations where the bacteria are endemic (10).

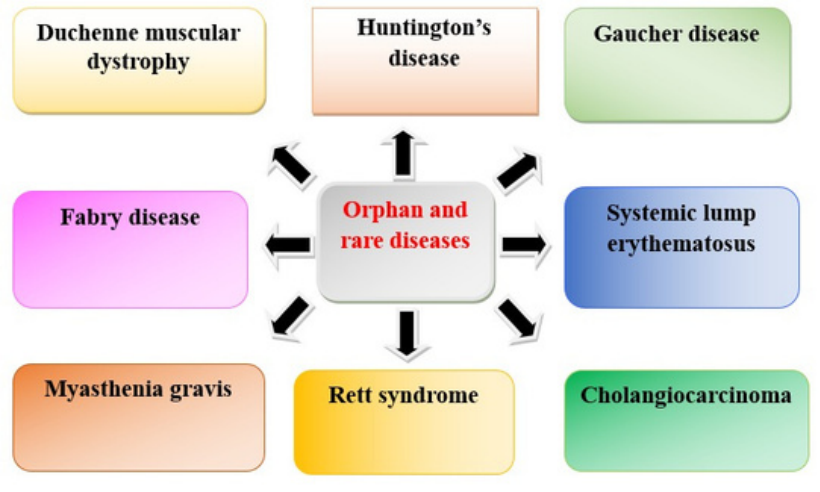

Figure 1. Some examples of orphan and rare diseases

2. Recognising rare and orphan diseases

A vast range of illnesses are included in the category of orphan and rare diseases, all of which are connected by the fact that they only afflict a small portion of the population. These illnesses are often distinguished by their infrequency, intricacy, and difficulties in diagnosis, treatment, and research. A number of important factors are involved in determining which diseases are orphan or rare:

2.1 Genetic basis

Numerous orphan and rare diseases can be caused by chromosomal abnormalities, mutations, or changes in specific genes. These genetic abnormalities can trigger a variety of clinical symptoms by messing with normal cellular functions (11).

2.2 Global impacts

Millions of individuals worldwide suffer from orphan and rare diseases, which are uncommon in and of oneself, affecting all ages, genders, and ethnicities. The stress that patients and their relatives experience from these illnesses is increased by the absence of adequate research funding and appropriate treatments. In addition to having a huge financial burden on society and healthcare systems, many illnesses cause terrible mental and physical pain for those who are affected (12). The fight against these requires increased public awareness, international cooperation, and advocacy for better research funding, diagnostic tools, and easier access to specialised treatment and therapies. By raising consciousness regarding orphan and rare diseases, we may work to improve the lives of individuals affected and advance research towards more effective therapies and treatments (13).

3. Difficulties in diagnosis and therapy

Monitoring rare and orphan diseases involves navigating a complex network of challenges, from the initial stages of diagnosis to ongoing treatment for these sometimes-fatal illnesses. The primary reason for these issues is the general lack of knowledge concerning orphan and rare diseases that permeates society, the healthcare system, and even the ranks of medical professionals. Due to their rarity and low visibility, many rare diseases remain poorly recognised or go undiagnosed, which results in significant delays before treatment can begin. Patients frequently find themselves in the middle of a painful and lengthy diagnostic process that involves visiting several different medical specialists and undergoing a battery of tests in order to get a precise diagnosis. This procedure frequently results in incorrect diagnoses, which stresses out patients and their families and produces therapies that don't work (14). Getting access to expert care and treatment is also one of the largest difficulties encountered by those with rare and orphan diseases. Treating these problems occasionally calls for interdisciplinary teams of experts, including pulmonologists, neurologists, geneticists, and others. However, there are situations when it is difficult to obtain this knowledge, particularly in poor or rural locations where treatment resources may be limited. The expense and availability of specialised diagnostic an procedures, therapies, and medications may also provide insurmountable challenges for a large number of patients, aggravating care inequalities and maintaining structural inequity in the healthcare system. A thorough and coordinated effort must be made on multiple fronts to address these complicated difficulties. Increasing public awareness of orphan and unusual illnesses and its policymakers' and healthcare professionals' understanding of them is essential to improving early recognition and diagnosis (13).

4. Prospects for the future and difficulties

Despite several challenges, there have been significant advancements in the field of orphan and rare illness studies that offer hope for the future. Advancement in precision medicine, computational biology, and genomics is transforming our knowledge of uncommon diseases. Researchers may now identify novel genetic variants, elucidate disease pathways, and create specialised treatments thanks to these advancements (4). Further encouraging innovation in rare illness research and drug development, expediting research findings, and facilitating data exchange are the growing collaborations among scientists, patient advocacy groups, industry partners, and governmental agencies However, numerous additional obstacles need to be , addressed before orphan and uncommon diseases can be fully treated (15). Lack of funding for research, uneven access to medicines and care, diagnosis delays, and the high cost of creating orphan pharmaceuticals are some of these challenges. Individualised approaches and customised treatment regimens are essential, as the variety of uncommon diseases poses significant obstacles to the production of efficient medicines that can help every patient (13). To solve these difficulties a financing and persistent collaboration from a range of sectors including government, business, academia, and patient advocacy groups will be required. Additional

cooperation and funding are needed to progress research, improve diagnostic capabilities, expand access to care and medications, and ultimately improve outcomes for patients with rare and orphan diseases. By working together to achieve common goals and making use of our collective expertise and resources, we can overcome the remaining challenges and pave the way for a better future for those with orphan and uncommon illnesses (15).

5. Conclusion

In order to sum up, fighting orphan and rare diseases necessitates concerted efforts to overcome challenges and benefit from new advancements in collaboration and research. Important challenges involve the necessity for continuous cooperation and funding in addition to the developments in genomics and precision medicine. Limited resources and uneven access are further issues. It is essential that we put out a call to action for increased awareness and support, pleading with interested parties to demand improved funding for healthcare access, education, and research. Working together and prioritising the needs of persons with rare and orphan diseases can greatly enhance results and standard of life.

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A bird eye view on Rasmussen Encephalitis


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Abstract

Rasmussen encephalitis (RE) is a rare and progressive neurological disorder primarily affecting children, characterized by chronic inflammation and unilateral brain atrophy. Diagnosis relies on clinical, electroencephalogram (EEG), magnetic resonance imaging (MRI), and histopathological criteria. Current treatments, including high-dose methylprednisolone, intravenous immunoglobulin's (IVIg), and surgical interventions such as hemispherectomy, offer varying degrees of success in managing seizures and slowing disease progression. Adalimumab has shown efficacy in reducing seizure frequency. Ongoing patent activity underscores efforts to develop novel therapies. Enhanced research is essential to improve diagnostic precision and treatment outcomes for RE patients. Keywords: Rasmussen encephalitis, diagnosis, treatment, seizures, hemispherectomy, adalimumab, patents, neurological disorder.

Keywords: Rasmussen encephalitis, Immunotherapy, Pathophysiology, Patents

1. Introduction

Rasmussen encephalitis (RE), first identified in 1958 by Theodore Rasmussen, is characterized by chronic inflammation of one hemisphere of the brain, leading to unilateral atrophy (1). This condition typically affects healthy school-aged children and is marked by persistent, medication-resistant focal seizures along with worsening neurological and cognitive deficits associated with the affected brain hemisphere. The disease significantly impacts patients and their families (1). Despite being recognized for approximately six decades, our understanding of RE remains limited, and available treatment options are still rudimentary. Due to the progressive nature of RE, early detection and diagnosis are essential for utilizing both current and emerging treatment strategies (2).

RE, also known as Rasmussen syndrome, is a rare central nervous system disorder marked by chronic, progressive inflammation of one cerebral hemisphere (3). This condition typically leads to frequent

epileptic seizures caused by uncontrolled electrical activity in the brain and gradual cerebral deterioration. Over time, additional symptoms may develop, such as progressive hemiparesis, language difficulties (if the left hemisphere is affected), and intellectual disabilities (3). The exact cause of RE remains unclear, but two leading theories suggest that brain inflammation might be either a response to a foreign antigen (infection) or an autoimmune disease confined to one side of the brain, leading to damage. RE primarily affects children aged two to ten, with the disease being most severe in the first 8 to 12 months. After reaching its peak inflammatory stage, the disease's progression usually slows or halts, leaving the patient with lasting neurological deficits (4). This article provides an updated overview of RE, detailing recent advances in understanding its pathogenesis and emphasizing clinical aspects critical to its diagnosis and management.

2. Clinical presentation

Rasmussen's Encephalitis (RE) is portrayed by uni-hemispheric brain shrinkage, focal drug-resistant epilepsy, developing hemiplegia, and deterioration of cognitive functions. RE generally starts in childhood or young adults with a mean age of 6 years at the time of presentation, in a previously healthy child. Seizures are often preceded by slowly progressive hemiparesis, hemidistonia, or hemiathetosis (5).

In most instances, seizures are polymorphic: in addition to simple motor seizures, there are almost all types of focal seizures that can occur. Seizure frequency that are resistant to antiepileptic drugs (AEDs) usually increases rapidly, and partial epilepticus may return. Epilepsia partialis cotinua (EPC) occurs in approximately half of children (5). During the illness, hemiparesis inevitably develops; at first, it is restricted to the postictal phase, but it quickly becomes permanent, albeit with varied severity, and it gets worse with increased seizure activity. Hemiparesis, which could include a dystonic component, stabilizes over time. Additionally, When the dominant hemisphere is compromised, symptoms include aphasia, cortical sensory loss, and hemianopia are developed (5,6). Like motor weakness, cognitive impairment is a consistent hallmark of RE and may initially be mild. Changes in behavior, such as irritation, emotional instability, or hyperactivity, frequently indicate the onset of mental illness. This includes learning disabilities as well as memory and attention issues. In the majority of patients, the degree of mental impairment appears to be correlated with how severe their epilepsy is, especially when it is related to the bilateral distribution of abnormalities in their EEG (5,6).

The sickness is progressing unabatedly. The natural history can be categorized into three stages: (1) a "prodromal stage," which lasts for months to eight years and is characterized by infrequent seizures; (2) an "acute stage," which often occurs close to the beginning of the disease and is characterized by frequent seizures, frequently in the form of EPCorstatus, and rapid neurological degeneration; and (3) a "residual stage," which has fixed neurological defects and persistent attacks that are less frequent.

3. Pathobiology

The histological features of RE include cortical inflammation, neuronal loss, and gliosis confined to one cerebral hemisphere. Multilocular inflammation is spreading throughout the hemisphere. Pathogenic signs include microglial and lymphocytic nodules, perivascular cuffing, neuronal death, and neuronophagia. Loss of neural cells, astrogliosis, and cortical cavitation are end-stage symptoms. On the other hand, recent imaging investigations validate long-standing pathology findings suggesting a preference for the fronton-insular region, with the occipital cortex being less frequently affected (6,7). Individuals who experience brain involvement typically have a higher sickness load and are younger. Heterogeneity and diversity in the lesion location, illness course, and degree of pathological abnormalities are crucial indicators of a disease process that affects multiple brain regions at different times. These differences are seen within and across individuals (5,7).

Neuroimmunology: Three types of immunopathological mechanisms are recognized to play a role in central nervous system (CNS) degeneration: antibody-mediated, T-cell cytotoxicity, and microglia-induced degeneration (6,8).

3.1 Antibody-mediated CNS degeneration

It has long been believed that the humoral immune system is untouched by the brain, but new research suggests this may not always be the case. Over the past ten years, it has been evident that circulating antibodies to neuronal surface proteins may be hazardous when they cause several CNS disorders. It has been evident during the past ten years that circulating antibodies to neuronal surface proteins are associated with several potentially fatal CNS disorders. Conversely, GluR3 antibodies were only discovered in a very few number of RE patients treated with plasmapheresis. A subset of individuals with RE had Munc-18-1 in their blood, even though this information was not disclosed. Despite being a signaling pathway neuronal protein required for synaptic vesicle discharge, Munc-18 is not thought to be a major target. Although evolutionarily conserved and an intracellular protein required for synaptic vesicle discharge, Munc-18 is not expected to receive much attention (6,9).

3.2 T-cell cytotoxicity

A significant role for cytotoxic T cells appears to be played in the etiology of Rasmussen's encephalitis. Ten percent or so of the inflammatory T cells are granzyme B-positive, and the majority of these cells are CD8. These granzyme B cells were discovered next to neurons and astrocytes, where the cytotoxic granules are polarized to face the target cell membrane; granzyme B discharge onto neurons has been observed on occasion. Moreover, spectra-typing of the T cells from the brain lesions revealed that these cells developed from distinct precursor T cells that responded to epitopes and were antigenic, indicating specificity for individual brain antigens. Cytotoxic T lymphocytes target neurons and astrocytes, one may assume that each of these cell types expresses an autoantigen. The antigen's identity is yet unknown, though (5–7).

3.3 Microglia-induced neuronal degeneration

One of the neuropathological features of Rasmussen's encephalitis is microglial activation. Although these cells' levels of activation can range between brain regions, they generally follow the stages of development and pattern of T-cell infiltration of cortical damage. Microglia play a role in the onset of seizures in various epileptic conditions through the release of pro-inflammatory cytokines and proteins such as interleukin. Additionally, complement-induced synaptic stripping, which can raise network excitability, is mediated by activated microglia. It is still unknown, though, exactly what pathogenic role microglial cells play in Rasmussen's encephalitis. Rasmussen's encephalitis also causes activation of astrocytes in addition to microglia. The progression of cortical injury is tightly correlated with the pattern of astroglial activity. Thus, astrocytes most likely play a comparable function in the inflammatory response in Rasmussen's encephalitis (6).

3.4 Inflammatory gene expression

To understand more about the composition of the immune response in cases with Rasmussen's encephalitis, the proportions of 86 mRNA transcripts associated with inflammation and Quantitative PCR were used to assess autoimmunity in 12 Rasmussen's encephalitis brains. The analysis demonstrated that greater levels of expression were seen for a selection of seven functionally relevant genes that code for interferon-γ, CCL5, CCL22, CCL23, CXCL9, CXCL10, and Fas ligand when comparing the cortical dysplasia cohort to the Rasmussen's encephalitis cohort. These genes cause activation of helper and inducer, memory, and effector T cells (6,7).

4. Diagnosis

RE is defined by a range of clinical signs and symptoms, none of which are individually diagnostic. Even though EPC is rare, it can occur in other conditions like Alpers syndrome. The diagnostic criteria proposed by Bien et al. include a combination of clinical presentation, EEG findings, MRI characteristics, and histopathological features, as summarized in Table 1 (10,11).

Table 1. RE diagnostic criteria

Part A: Clinical, EEG, and MRI	
Clinical	Focal seizures and deficits in one cerebral hemisphere.
EEG	Significantly lateralized slowing of brain activity and seizures originating from one side
MRI	Pronounced focal cortical atrophy on one side of the brain and at least one of the following: 1. Hyperintensity in gray or white matter on T2/FLAIR (fluid-attenuated inversion recovery) imaging. 2. Atrophy or hyperintensity in the ipsilateral caudate head on T2/FLAIR imaging.
Part B: If not fulfilled Part A	
Clinical	EPC or Progressive* unilateral cortical deficits
MRI	Progressive* and significantly lateralized cortical atrophy
Histopathology	T-cell–dominated encephalitis with activated microglial cells (often forming nodules) and reactive astrogliosis; the presence of numerous parenchymal macrophages, B-cells, plasma cells, or viral inclusion bodies excludes the diagnosis of RE

Progressive*: It indicates that there have been at least two consecutive examinations or studies; italics suggest recommended changes.

5. Recent advancement in treatment (6,9,11)

5.1. Medical management

- High-dose methylprednisolone (MP), IVIg, plasmapheresis, or immunoadsorption: variably effective in seizure control and may slow disease progression temporarily.
- Calcineurin inhibitors (e.g., tacrolimus): shown to slow hemiatrophy progression and reduce cognitive decline but not effective for seizure control.
- Combination therapies (e.g., steroids, IVIg, tacrolimus, mycophenolate mofetil, cyclophosphamide, alemtuzumab, methotrexate, rituximab): mixed short-term success reported in various case studies.
- Adalimumab: reduced seizure frequency by more than 50% in some patients and stabilized neurological decline in a few cases.

5.2. Surgical management by Hemispherectomy and hemispheric disconnection (HD) in RE

- Hemispherectomy and HD are the only established methods to cure RE seizures, with success rates of 70–80%.
- Advances in neuroimaging and neuroendoscopy have improved HD techniques, minimizing risks.
- Common HD techniques:
  - Modified functional hemispherectomy
  - Peri-insular hemispherectomy
  - Parasagittal hemispherectomy
  - Endoscopic-assisted hemispherectomy
- HD requires technical expertise and carries a risk of incomplete disconnection

6. Patents

The patents related to the management of the disease are mentioned in table 2

Table 2. Summarizes an update on patents on RE

S. No.	Patent Number	Title	Year	Status	Ref
1.	EP2490691A1	Use of 1h-quinazoline-2,4-diones	2012-08-29	Withdraw	(12)
2.	WO2011048150A1	Use of 1h-quinazoline-2,4-diones	2011-04-28	Published	(13)
3.	CA 2698831	Use Of A Peptide As A Therapeutic Agent	2010-03-08	Dead	(14)

7. Conclusion

Rasmussen encephalitis (RE) presents challenges in diagnosis and management due to its rarity and progressive nature. Diagnostic criteria include clinical, EEG, MRI, and histopathological features. Recent treatments like high-dose methylprednisolone, IVIg, and surgical interventions show promise but with varying success rates. Adalimumab has demonstrated efficacy in reducing seizure frequency. Surgical methods like hemispherectomy boast success rates of 70–80% but require expertise and carry risks. Ongoing patent activity indicates continued interest in developing therapies. Further research is needed to enhance diagnostic accuracy and treatment effectiveness for RE.

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Misconception and challenges of rare disease in research and development of orphan drugs



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Abstract
Rare diseases are those diseases which affect quality of life of both patient and their families. The greatest concern of research and development of pharmaceutical industries is to develop the drug for such disease which is commonly called as orphan drugs. Rare diseases are not at all rarely occurring diseases. In developed countries like Europe and America 25-30 million of patients are suffering from rare diseases and there are about 4000-5000 different types of rare diseases. Several factors have created a challenge and burden on R&D and pharmaceutical industries for upshot of drugs for these diseases. But it's been a misconception that pharmaceutical industries are neglecting such rare diseases because of lack of understanding the mechanism of these diseases, unavailability of patients for clinical trial purpose, high investment in R&D. But the fact is that investment by industries on R&D for orphan drugs is rising day by day.

Keywords: Rare diseases, orphan drugs, R&D, misconception.

1. Introduction

Rare diseases are uncommon and generally don't occur in many patients. The signs and symptoms of these diseases are diversified varying from person to person and disease to disease. There above 8000 types of rare disease. It is been estimated that 350 million people throughout the globe are suffering from rare diseases and in India almost seven crore people are suffering from rare disease. In state of Karnataka alone 3-40 million people are suffering from rare diseases. Therefore, the need of sustainable improvement in treatment of rare diseases is priority for pharmaceutical industry to develop orphan drugs. The upshot of orphan drugs led to many misconceptions like pricing of drug, rarity of disease and its impact on healthcare system (1). The regulations for orphan drug were introduced in the year 2000 in Europe which further extended to Japan and other countries. Today there are about 1000 orphan drugs to cure rare diseases, due to which there is a tremendous increase in the expenditure of R&D and orphan medical products (2).

2. Misconceptions encountered

2.1 Price of orphan drugs

Commonly, it was assumed that price of orphan drugs is comparatively high than non-orphan drugs. Orphan drugs are categorised into four different categories (3):

- The oncology group includes drugs which are generally used in multiple cancers. As compared to others, oncology treatment of rare disease is higher but effective from clinical point of view. It covers 44% of orphan and rare disease drugs.
- The repurposed drug that are approved for common indication that are extended by rare disease indication. They are 10% of approved orphan and rare disease drugs.
- The second to market rare disease treatment which covers 16% of approved orphan drug.
- The first to market non-oncology drugs which cover 30% but are not used as standard of care due to less effectiveness.

In all the four categories, it is utmost difficult to determine the price of orphan drugs for rare disease. The average price of oncology category per cycle is 34,000 Euros. For non-oncology and repurposed category, it is between 16000-24000 Euros. 70% of orphan drugs have low price and only 30% are higher price for rare diseases (4).

2.2 Impact on healthcare budget

Due to high price of orphan drugs it has prominently impacted affordability for health care budget. To justify this, the budget impact in Europe is 1-4.6% for rare disease (5). Moreover, population treated for rare disease is more that affects affordability. Data shows that budget for rare disease will be 4-6 % only in the next 5 years (6). Healthcare managers have observed that orphan drugs with high price are a big challenge for healthcare budget (7). In this concern, the price of orphan oncology drug is lower than non-orphan oncology drugs, and the population is also small and constricted.

2.3 R&D investment

Lot of investment is needed in R&D of orphan drugs and returns are also favourable. The specific legislative investment decided by regulatory has made it possible to invest in R&D for orphan drug discovery (9). Most importantly the development of orphan drug is generally a lengthy process which requires lot of substantial investment. Other key constituents are overall capital, success of development, time & other cost apart from R&D (8).

2.4 Manufacturing cost

The manufacturing cost of orphan drugs is higher than non-orphan drugs. Manufacturing cost of orphan drug depends on R&D investment and there is no other criteria like for non-orphan drugs. Pharmaceutical industries make profit to reinvest in other new medicines. Major factors are financial investment that require bringing product into the market, treatment efficacy, budget among others. Final drug price depends on the negotiation with government bodies, wholesalers, insurers, etc.

2.5 Excessive financial return

Companies involved in manufacturing drugs for rare and orphan disease yield financial return due to high price of drug products. It is been estimated that within ten years 11% is recovered (10). If 100M$ is invested in R&D it will generate 618M$ after 10 years with 11-14% of return. According to regulation, industries investing in R&D and marketing of orphan drugs take valuable incentives (11) and the main focus must be on patent protection.

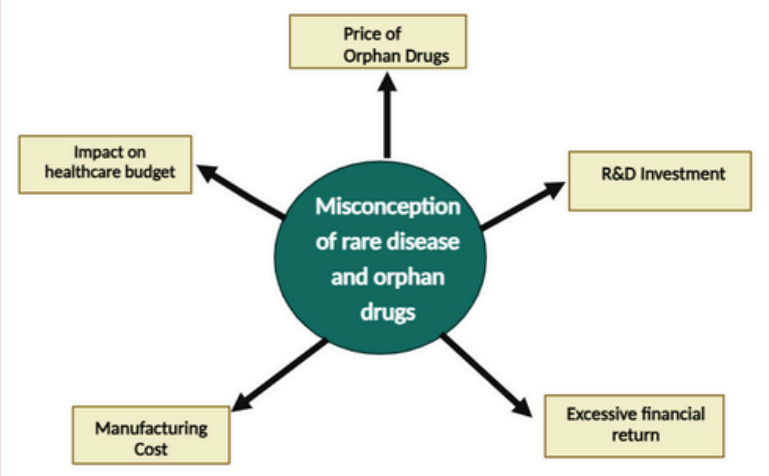

Figure 1. Misconceptions of rare disease and orphan drugs

3. Challenges of rare disease

The main challenge in rare disease is number of people affected by rare disease and their families suffering from undiagnosed cases, optimum care, lack of knowledge, unviability of physicians and improper guidelines.

3.1 Challenges to patient

The challenges faced by patient is finding proper physician to treat the disease, patients experiences on manifestation of disease, since they are unaware of conditions and its management. The price of drug available is a major challenge. Like in alpha 1- antitrypsin deficiency patients face lung dysfunction. Diagnosis is also delayed that increases the burden of rare disease and the available augmentation therapy is also very high.

3.2 Challenges to physicians

The management of rare disease is very difficult and major hurdle for physicians. The issue arises from unavailability of clear and accessible guidelines**.** Another challenge is geographical diversification of centres that provide treatment of rare disease which increase expenses of travelling.

3.3. Challenges to investigator

Investigators who are studying rare disease faces challenge in assembling cohorts of rare disease, availability of orphan drugs, funding for research and development (12).

4. Solution to these challenges

Patient advocacy organizations are working hard to provide optimal care to patients and families suffering from rare disease. Such organizations have collaborated with clinicians, physicians, government authorities, and pharmacist in building research. Examples of such organization are Alpha 1 Foundation, HHT Foundation, National Organization for Rare Diseases, Cystic Fibrosis Foundation, LAM Foundation. These foundations are focusing on finding cure of rare diseases. The success of these organizations hinges on fundraising support for research and development of orphan drugs. They also provide electronic consultancy and assist self-education of the patient on managing rare disease. Skype follow up are also available to patients through these organizations. Most importantly they provide funds for R&D. Example Orphan Drug Development Grant Program of Food and Drug Administration and Rare Disease Clinical Research Network for National Institute of Health (12-14).

5. Conclusion

Misconception regarding orphan drugs used for rare disease puts light on R&D, affordability and value of orphan drugs. Rare diseases are new concern to pharmaceutical industries and major challenge in exploring new treatment. For ensuring the success of rare disease R&D, it must appreciate and reward innovators. There are lots of misconceptions that are encountered regarding rare disease and orphan drugs related to manufacturing cost of drug, investment in R&D, impact on healthcare budget, price of orphan drugs, etc. But these all are misconceptions and the reality is far different because all these criteria are same for non-orphan drugs as well. There are various challenges faced by patients, physicians and investor like patients are unaware of disease, management of disease is difficult, manifestation of rare disease, etc. But patient advocacy organization is working towards resolving all the challenges by providing and collaborating with care association like government authorities, health sector, physicians, and clinicians.

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Comprehensive review of orphans drugs and neglected disease


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Abstract
Rare diseases, also referred to as "orphan diseases," present serious health challenges, especially for newborns, infants, and children under the age of five. These diseases, which are largely genetic (around 80%), affect a small percentage of the population globally—0.65% to 1% according to WHO. Definitions vary by region, with each area setting its own criteria for what constitutes a rare disease. Protozoan diseases such as Human African Trypanosomiasis, Chagas disease, and Leishmaniasis result in severe health issues, including chronic organ damage and death. Similarly, helminth infections, including soil-transmitted helminths, schistosomiasis, and lymphatic filariasis, impact millions worldwide, causing significant morbidity and disability. Diagnosing rare diseases is difficult due to limited knowledge and diagnostic tools. However, the advent of Next Generation Sequencing (NGS) has greatly improved the speed and accuracy of diagnosis. Genetic testing methods like Trio Exome Analysis, Whole Exome Analysis, Clinical Exome, and Targeted Gene Panels are instrumental in identifying genetic variations and aiding diagnosis. Developing treatments for rare diseases is challenging due to the small patient populations and high costs. Overcoming these hurdles requires enhanced international and regional collaboration, increased awareness and training for healthcare providers, and the creation of standardized diagnostic protocols. Adjusting clinical trial regulations to better address the unique needs of rare diseases, while maintaining safety and quality, is crucial for advancing treatment development.

1. Introduction

Rare diseases, often known as "orphan diseases," are serious threats to life, especially for newborns, infants, and children under five. The term "orphan disease" is fitting for several reasons. Firstly, these diseases affect vulnerable groups like newborns and young children disproportionately. Secondly, it implies that these diseases often don't receive the attention and resources needed for their control. According to the World Health Organization (WHO), rare diseases affect 0.65% to 1% of the population. Around 80% of these diseases have genetic roots, with half of them impacting children, and sadly, 30% of these young patients don't survive beyond five years. Different regions have slightly different definitions for rare diseases. WHO defines them as life-altering disorders affecting 1 or fewer in every 1000 people. In the United States, rare diseases are those that affect fewer than 200,000 individuals. In Japan, they're conditions with unknown causes and no effective treatments, affecting fewer than 50,000 people and imposing significant financial and emotional burdens. South Korea considers diseases rare if they affect fewer than 20,000 people or if there's no suitable treatment available. Taiwan defines rare diseases as those affecting fewer than 1 in every 10,000 individuals, with a genetic basis and challenging diagnosis and treatment. In China, rare diseases affect fewer than 1 in every 500,000 individuals or have a neonatal mortality rate of fewer than 1 in every 10,000 births (1-7).

1.1 Protozoa causing disease

1.1.1 Human African trypanosomiasis (HAT)

In HAT, The starting stages are marked by cervical lymph node that are swelled, known as Winterbottom's sign. Other symptoms include fever, headaches, and lymph node swelling. Over time, the term "sleeping sickness" emerges due to night time insomnia and daytime drowsiness, despite no overall change in total sleep duration. Changes in personality, , and movement abnormalities reminiscent disease of Parkinson's may also occur and cognitive decline. Due to the progression of the disease, there's a gradual deterioration in brain function, leading to coma and eventual death (8).

1.1.2. Chagas disease

It is also being spread to wealthier nations through international migration. The culprits behind its transmission are the nocturnal "kissing bugs," scientifically called as triatomine bugs, which hide in wall crevices or among livestock. Acute infections typically manifest as a moderate fever that resolves on its own. However, Chagas disease that is chronic affecting around 30% of those infected, have health risk that are serious. It mainly affects the gut, leading to conditions like megaesophagus or reactivation of latent infections, which can result in severe cardiac and neurological complications. Additionally, the heart can be impacted, causing cardiomyopathy and irregular heartbeats (9-11).

1.1.3. Leishmaniasis

The causative agent for different diseases is Leishmania. Leishmaniasis is cutaneous and global, often resulting in chronic skin ulcers. Initially, a small bump appears a few weeks after infection, which then progresses into a sore, and eventually forms an ulcer with raised edges. In some cases, the lesion may spread to other parts of the skin or even to the nasal mucosa, causing severe damage to the face and airways, which can be life-threatening.

Visceral leishmaniasis (VL), also known as "kalaazar," can lead to severe complications such as weakened immune system, enlarged spleen, bleeding, and ultimately, death. HIV co-infection makes leishmaniasis even more severe, with recurrent illness even after treatment unless HIV is managed properly.

1.2 Diseases caused by helminths

Helminths, or worms, have been known to humans since ancient times. Soil-transmitted helminths (STHs) along with filarial worms causing diseases like dracunculiasis, river blindness, and LF, pose significant health risks (12-18).

1.2.1 Soil-transmitted helminths

Soil-transmitted helminth infections (STHs) is characterized as an illness group, that are contracted when people either ingest or come into contact with soil containing worm eggs or larvae.

These worms follow similar life cycles, entering the gastrointestinal tract, reproducing, and releasing eggs through faeces. However, hookworms differ from Ascaris and Trichuris in that their larvae become infectious in the soil before penetrating intact skin to begin the parasitic phase, rather than being acquired through egg ingestion (19-24).

1.2.2 Schistosomiasis

Infected snails release cercariae into the water can penetrate human skin and enter the bloodstream. They migrate to the mesenteric veins or the perivesical venous plexus via the liver and lungs. These parasites remain in the blood vessels for their entire lifespan.

Individuals may develop acute symptoms like fever, fatigue, and eosinophilia may develop after few weeks, known as "Katayama fever." Schistosomiasis comes from eggs getting trapped in the liver or lungs, causing inflammation are the major impact of health. Eggs can lead to complication complex by penetrating into blood vessel walls, ureters, bladder, and intestines. Mesenteric schistosome infections can cause periportal fibrosis, portal hypertension, ascites, and varices. Eggs are eventually released in faeces or urine. Globally, about 200 million people are infected, with illness severity varying across different regions (28-31).

1.2.3. Filariasis

Chronic illness caused by a transmitted parasite by mosquitoes is known as filariasis .It is caused by three species of roundworms: *Brugia malayi, Wuchereria bancrofti, Brugia timori*, and spread by five mosquito species: Anopheles, Aedes, Mansonia, Culex and Ochlerotatus.

Wuchereria and Brugia worms are similar but differ in size, body structure, cuticle thickness, and appearance. Adult worms are found in lymph nodes, while microfilariae are seen in the blood, detectable through a blood smear stained with Giemsa or H&E. Microfilariae are 200-300 micrometers long and 2-8 micrometers in diameter, identifiable by their tail nuclei (32-35)

2. Challenges

Defining rare diseases is not straight forward. These are often serious, long-lasting conditions that can shorten life expectancy. As of 2019, there are about estimated to be around 6,000 to 8,000 rare diseases. Some affect only a small number of people, while others impact larger populations, like sickle cell anemia, which is prevalent among individuals of African, Middle Eastern, and Asian descent but less common in other regions. A disease might be rare in one part of the world but more prevalent elsewhere (36,37).

3. Complications

- Not fully understanding the pathophysiology of the disease
- No models established
- There is no standard drug available for comparison of therapeutic efficacy
- Not exact knowledge of how the disease progresses during the course of time
- There is a lack of clear guidelines for diagnosing the disease

4. Incentives

In many countries, developing drugs for rare conditions relies on support from the government. Different places have special agencies overseeing this. These agencies offer perks like faster approvals, fee waivers, and exclusive rights in the market to encourage research into these specialized drugs. This fee waiver announced by Central drug standard control organization if drugs are already approved particularly focuses on drugs for rare diseases and for diseases where there is no existing treatment available (38-48).

5. Challenges in diagnosis

Around 80% of rare diseases are genetic and usually affect children. Due to limitation in diagnostic method diagnosing these diseases is challenging. However, with the advancement of Next Generation Sequencing (NGS) technology, detection has become faster and more accurate, providing precise results within 4-8 weeks, compared to previous years. NGS techniques like Whole Exome Sequencing, Whole Genome Sequencing (WGS), and Clinical Exome can provide early identification of rare disease genes.

Research and development for rare diseases face major challenges due to limited knowledge about their pathophysiology and natural history. Due to lack of published data on long term, hence Long-term follow-up is crucial as many rare diseases are chronic. Clinical trial norms should also be reviewed and adapted to address the specific challenges of rare diseases while ensuring the safety and quality of drugs and diagnostic tools.

5.1 Diagnosis of rare disease

Early diagnosis of rare diseases early is a real challenge because of various factors. Many primary care doctors are not aware of these conditions, and there are not enough screening or diagnostic facilities available. The traditional genetic tests available can only cover a small number of diseases. There is lack of awareness about rare diseases among the general public .Many doctors do not have the right training or do not have the requisite knowledge about these conditions to diagnose and treat them correctly and quickly. Waiting so long for a diagnosis, or getting the wrong one, can make things much harder for patients.

5.2 Genetic test types

There are various types of genetic tests used to diagnose rare diseases (49-51):

5.2.1 Trio exome analysis

This test helps identify genetic variations that are either newly occurring (de novo) or inherited from parents. It typically involves analysing the genetic makeup of both affected and unaffected family members, such as parents and patients.

5.2.2 Whole exome analysis

This comprehensive test examines all the sequences within the exome, which are the parts of the genome that code for proteins. It provides a thorough overview of genetic variations across the entire exome.

5.2.3 Exome of clinical

It focuses specifically on genes implicated in human disease, offering a targeted approach to diagnosis.

5.2.4 Targeted gene panel

This test involves analysing a selected set of gene regions or individual genes known to be associated with certain diseases. It allows for a more focused examination of specific genetic markers relevant to particular conditions.

6. Treatment

Genome analysis plays a crucial role in diagnosing various diseases nowadays. Due to advancements in gene transfer therapies, we have recorded seeing success in treating patients. These therapies often involve using viral vectors to replace missing genes, effectively correcting genetic defects. Another approach involves modifying or blocking disease-causing proteins using gene disruption technologies In the case of cancer, treatments can involve modifying immune cells, known as chimeric antigen receptor (CAR) T cells, through gene-modified cell therapy. This approach boosts the ability of the immune system to target and destroy cancer cells. Cutting-edge technologies allow for direct modification of genes, both in vivo (inside the body) and ex vivo (outside the body), through gene editing. These technologies hold tremendous promise for treating a wide range of diseases by precisely altering genetic sequences. The main challenges in the treatment include prohibitive cost and unavailability of treatment (51-53).

7. Conclusion

Rare diseases, often termed "orphan diseases," pose significant challenges due to their complex nature, limited patient populations, and the substantial resources required for their diagnosis and treatment. Affecting 0.65% to 1% of the global population, these diseases are predominantly genetic and have a profound impact on newborns, infants, and children under five, with a significant proportion not surviving beyond early childhood. The variability in definitions across different regions highlights the global challenge in standardizing approaches to these conditions. Protozoan and helminth infections, such as Human African Trypanosomiasis, Chagas disease, Leishmaniasis, and various soil-transmitted helminths, contribute significantly to the morbidity and mortality associated with rare diseases. These infections often lead to chronic conditions, severe organ damage, and death, underscoring the need for improved diagnostic and therapeutic strategies. The advent of Next Generation Sequencing (NGS) technologies, including Whole Exome Sequencing and Targeted Gene Panels, has revolutionized the diagnosis of genetic rare diseases, enabling faster and more accurate identification of genetic mutations. Ultimately, advancing the

understanding and treatment of rare diseases requires a multifaceted approach, involving increased awareness, better diagnostic tools, standardized clinical protocols, and innovative therapeutic strategies. By addressing these challenges, we can improve the quality of life for those affected and ensure that rare diseases receive the attention and resources they deserve.

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Essential drugs for rare diseases

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1. Introduction

Pharmaceutical companies or institutes introduce several drugs in the market after authorization by regulatory agencies of the respective country. The drug which comes first in the market is called as prototype drug and other related drugs with similar mechanism of action are called as congeners. Each pharmaceutical company obtains a patent on that congener and can market it exclusively till the end of patent life of that drug. Once the patent life is over, other pharmaceutical companies can market the drug with a generic name or their own trade name. Every new drug is given a new international non-proprietary name (INN) by an international body. The INN is also called as generic name of the drug, while every company can give a trade name for their own drug and is called as Brand name. As a result of market competition and a desire of promoting their own brand names, there are few thousand drugs with their own INNs and brand names in the global market.

In 1977, World Health Organization (WHO) suggested the concept of Essential Drugs. What WHO argues is "All such drugs, introduced in the global market are not necessary for majority of patients. Therapeutic needs of majority of patients can be met with selective few hundred drugs. These selective drugs, which can satisfy priority health needs of the majority of patients are termed as Essential Drugs by WHO"
The first list of Essential drugs was published by WHO in 1977. Every alternate year WHO revises the list. The latest 23rd edition of WHO essential drug list was published in 2023. From the year 2007, WHO has started publishing a separate list of essential drugs for children and 9th revised model list of essential drugs for children was published by WHO in 2023. All these lists are in public domain and any interested person can download them.

Every country can adopt a list of essential drugs based on WHO guidelines and can modify them as per their priorities. More than 170 countries all over the world have accepted the WHO concept and some of them have developed their own list of essential drugs. India has revised its list of essential drugs in the year 2022. The list was revised after 2015. The latest Indian list contains 384 essential drugs.

2. Economics of new drug development

Development of a new drug is a costly and adventurous decision, at least in an economic sense. It is usually advocated by international associations of pharmaceutical industries that development of a new drug costs them around 1 billion dollars ($). In terms of Rupees, it turns out to be 8500/crore Rupees. ($1 = Rs.85). A pharmaceutical company will invest this huge amount with the only expectation that they will plough back the invested amount after marketing permission to the drug. This is possible only if there are more patients, available for treatment of that indication. If the number of patients is small, then the price of a new drug can be prohibitively high making it unaffordable to the patient population. It is known that some drugs can cost as much as few million US $ per year in USA making it few crore Rupees annually if the drug is imported in India. This is unaffordable even for a prosperous family. Spinraza (Nusinersen), used for spinal muscular dystrophy costs $ 375,000 (Rs. 3.2 Cr.) per patient. Migalastat, used for Fabry's disease costs $ 310,000 (Rs. 2.63 Cr.) annually.

Unless the drug is accessible and affordable, an average family cannot use it especially if it is to be given repeatedly and more so if the entire expense turns out to be Out-of-Pocket (OOP). This is very much true in a country like India where it is mentioned that a fraction of population, every year goes below poverty-line only because the cost of treatment in unaffordable.

3. Rare diseases

The logic is very relevant in case of "Rare" diseases. There are various definitions of rare diseases in different countries and continents; but WHO defines rare diseases as "if 1 in 2000 persons are affected by the condition, then it can be termed as a rare disease". It is estimated that 300 million people are affected by rare diseases globally. It is also indicated that about 7-8 % of the population is affected by rare diseases. Nearly 5000 to 8000 rare diseases are known. These are identified in "Orphanet" a global online list of rare diseases. One latest estimate indicates the number of rare diseases to be 10,000 in number. In India, with a population of around 1.4 billion at least 100 million (10 crore) Indians are expected to be affected by rare diseases. It means one third of global population of rare diseases resides in India. Out of all rare diseases, around 400 rare diseases have been reported in India; but it is only tip of the iceberg.

Rare diseases are challenging to diagnose and treat for a number of reasons, particularly in India. First and foremost reason is that it is difficult to know, especially for parents of a child that their child is having a rare disease. A rare disease like Autism may not show expression till the age of 2 to 3. Further, parents may find symptoms of rare diseases as a delay in growth which may be found even in a normal child. The parents may take a child to a doctor later than recommended. The diagnosis of rare diseases is not simple because biomarkers for the diseases are not known in every case. Not all rare diseases are of pediatric nature. It is reported that about 80 % of rare diseases are of genetic origin and 50 % of the patients are children. It is further reported that 35% of the patients die before the age 1; 10% die between the age 1 to 5 and 12% die between the age 5 to 15. Treatment for all rare diseases remains elusive because pathophysiology of many rare diseases is not fully understood.

Thankfully, in 2021, a Policy for Rare Diseases has been launched by the Government of India. According to the policy, rare diseases seen in India are divided into three groups.

- Disorders that may be cured with just one therapy.
- that need long term treatment which is available at low cost, with documented evidence and require annual or frequent monitoring.
- Diseases requiring lifelong therapy where definitive treatment is available at high cost, but selection of right patient to benefit is challenging.

The policy document contains a list of rare diseases, however it is not comprehensive and might evolve in the future. Every group involves a list of specific diseases. For diseases specifically falling under group 3, the Government of India offers one-time financial assistance which was initially set at Rs. 20 Lakhs, but recently amended to Rs. 50 Lakhs.

Rare diseases exhibit various distinguishing traits. A few of them are listed below.

- Rare diseases are chronic, often degenerative, fall in the severe or very severe category, and are mostly life-threatening.
- About 50% of rare diseases develop in childhood.
- Disabling; the quality of life of individuals with uncommon diseases is frequently impacted by the lack or loss of autonomy.
- High psycho social burden: the suffering of patients with rare disease is exacerbated by psychological despair, the lack of therapeutic optimism and/or actual assistance for everyday living.
- Rare diseases can often be incurable due to the lack of appropriate therapeutic options. Symptomatic treatment may improve quality of life or life expectancy in some cases.
- Management of rare diseases is an ongoing challenge and families struggle to find appropriate care.

4. Some important observations

4.1 In 1981, National Organization of Rare Diseases (NORD) was formed in 1981 to take care of interests of persons with rare diseases in USA.

4.2 In 1983, USA became the first country to enact Orphan Drugs Act and offered incentives to pharmaceutical companies who manufacture “Orphan Drugs” acting on rare diseases. The Rare Diseases Act was passed in 2002 and by January 2020, USFDA approved 564 orphan drugs to treat 838 rare diseases.

4.3 In 1985, Japan and in 1997 Australia passed similar acts following USA.

4.4 In 2000, European Union passed The Orphan Medicinal Product Regulation (Regulation (EC) No 141/2000 and was followed by action plan on rare diseases in 2009. By March 2021, 260 medicinal products in Europe had market authorization for the treatment of rare diseases.

4.5 Various associations of stakeholders related to rare diseases have been formed. In Europe and 1000 rare-diseases related patient organizations together formed EURORDIS (the European Organization of Rare Diseases)

4.6 In December 2021, United Nations adopted a resolution, emphasizing importance of dealing with rare diseases, and requested member countries to take appropriate steps to provide affordable, accessible and good-quality care facilities for children and other dependents living with a rare disease and measures promoting the equal sharing of household responsibilities.

4.7 People living with rare diseases (PLWRDs) from all around the world, came together to form Rare Diseases International (RDI). More than 90 member organizations from 46 different nations make up RDI, which in turn represents patient groups with rare diseases in more than 150 countries worldwide.

4.8 In February 2017, International Rare Diseases Research Consortium (IRDiRC)defined its vision and identified three goals to be achieved by 2027 (1). The Rare Disease Treatment Access Working Group (RDTAWG) was established with three aims:

(1) To raise the standard of care for patients with rare diseases through facilitating the access to approved medications.

(2) To initiate research into the barriers to accessing medications for rare diseases, especially in low- and middle-income countries (LMICs).

(3) To identify opportunities to remove these barriers.

Based on various international databases, they have identified 204 essential drugs which can be used for treating different rare diseases (2).

4.9 Looking at the cost of developing a new drug (Rs. 8500 Cr.), limited market, and relatively less number of patients with rare disease, it is less likely that any pharmaceutical multinational company may launch an exclusive set of efforts for developing a new drug; as it may not be financially attractive. Still, in the USA, passing of Orphan Drugs Act has resulted in development of 564 orphan drugs due to incentives. As a result, next viable alternative is to explore if any of the existing approved drug can be repurposed for the treatment of rare disease(s). Since safety of existing approved drugs is established by regulatory authorities, cost of re purposing a drug for a rare diseases stays low. Pre-clinical and phase 1 clinical studies need not be repeated. What we need is only phase 2 and phase 3 clinical studies followed by marketing authorization from the regulatory authorities.

4.10 The Government of India has approved drugs related to four genetic diseases for marketing in India. The diseases are: Tyrosinemia, Gaucher disease, Wilson’s disease and Dravet-Lennox Gestaut Syndrome. Now drugs for these diseases will be available at a fractional price in India as compared to their international counterparts. Approvals for four more diseases are in pipeline. Some of the Indian pharmaceutical companies also have shown interest in providing drugs related to rare diseases in India.

Names of some of the rare diseases observed in India are mentioned as an illustration: Autism spectrum of disorders (ASD), Cockayne syndrome, Hemophilia, Thalasaemia, Sickle cell anemia, Fabry's disease, Gaucher disease, Pompe disease, Systemic Lupus Erythematosus (SLE), Autoimmune disease, Spinal Muscular Atrophy (SMA), Tyrosinemia, Phenylketonuria.

5. Conclusion

After declaration of policy for rare diseases by Government of India, few Indian pharmaceutical companies have started developing medicines for rare diseases at affordable prices. In future, we can expect that affordable treatment for few rare diseases will be a reality in India.

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Rare diseases overview for a clinical trial perspective



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1. Introduction

Rare diseases are those diseases which affect a very few number of people. They are also termed as orphan diseases and are associated with improper management, long term deterioration, adverse effects and fatalities as well. As per the Committee for Orphan Medicinal Products (COMP), European Medicines Agency (EMA), a disease can be categorized as a 'rare disease'(RD) when the number of affected individuals is less than 5 members across 10,000 individuals in the European Union EU (1). The United States Food and Drug Administration (USFDA) designates a disease as 'rare' if the number of people in the USA suffering from it are less than 2,00,000 i.e. less than 6.4 persons in 10,000 (2). The WHO specifies it as a condition occurring in 1 or lesser persons per 1000 individuals. India has not given any specification for disease categorization based on prevalence but segregated based on treatment/management options (3). In case where fewer than 2 patients among 100,000 suffer from a disease, then it is termed as an 'ultra-rare' disease (4).

2. Rare disease burden

In the EU 6000 - 7000 RDs have been identified, most of them being of genetic origin. Although a RD affects very less individuals, together RDs affect approximately 30 million in the EU and 9, 20,000 people in Spain as per 2022 data (5). In the USA too, 7,000 RDs affect more than 30 million people (2). India has around 100 million patients suffering from RDs. In addition to the global count of 7000-8000 known RDs India reports 450 more (6). Africa too is no exemption to these numbers related to RDs. 80% of RDs have been identified to have genetic origin, and 50–75% being paediatric onset (7,8).

Quantification of the prevalence of RDs itself has been a challenge due to lack of awareness, the disease being undiagnosed and unreported /under reported. Currently healthcare systems make wide use of electronic medical record (EMR) systems to perform studies effectively across large sections of population in order to identify and characterize individuals with RDs. The team from Clinical Sequencing Exploratory Research (CSER) and Electronic Medical Records & Genomics (eMERGE) employed genomic information from the EMR data and identified the subjects with RDs (9). However, it has been noticed that genetic information still had missing ends.

Tsevdos, D. *et al*. (2024) developed an innovative digital phenotyping algorithm to find out from the EMR, paediatric subjects who had a high probability of being susceptible to genetic disorders, thus aiding to provide appropriate treatment and avoid errors. They also addressed about PheIndex algorithm, which is a boon to detect rare genetic disorders in children, thereby solving the problems such as under diagnosis and delayed diagnosis issues (10).

3. Classification of Rare Diseases

RDs may be categorized in various ways. Table 1 below presents some RDs based on the organ system affected.

Table 1. Brief list of organ system wise categorization of RD

S. No.	Category	Disease name	Remarks	Ref.
1.	Allergic and Immunologic disorder	Agammaglobenemia or hypogammaglobulinemia	Characterized by low or absent mature B cells, occurs in infants around 6 months age	(11)
2.	Cardiac and vascular disorders	Eisenmenger syndrome	Untreated congenital cardiac defects leading to pulmonary hypertension and cyanosis	(12)
3.	Endocrine and metabolic disorders	Gaucher's disease	Genetic disorder - deficiency of the enzyme glucocerebrosidase	(13)
4.	Gastroenterologic conditions	Dubin-Johnson syndrome	Genetic disease -mutations in the bilirubin transporter MRP2 leading to jaundice and conjugated hyperbilirubinemia	(14)
5.	Hematologic disorders	Paroxysmal nocturnal hemoglobinuria	Acquired hematopoietic stem cell (SC) disorder which leads to the lysis of red blood cells, hemoglobinuria, thrombotic events, etc.	(15)
6.	Skin and soft tissues conditions	Epidermolysis bullosa	Genetic dermatoses characterized by mucocutaneous fragility and blister formation	(16)

The other categories include rare bacterial, fungal, viral, parasitic disorders; rare nutritional, congenital, environmental, psychological, newborn diseases; chromosomal aberrations, chromosomal disorders; glycogen storage & lysosomal storage disorders and many more (6).

The National Policy on Rare Disorders (NPRD) 2021 segregated and described elaborately RDs based on clinical considerations. A brief summary is given below (3).

Group 1: Diseases suitable for a one-time curative treatment like SC transplantation (e.g. Lysosomal storage disorder, etc.), organ transplantation (e.g. Fabry disease, maple syrup urine disease, etc.)

Group 2: Diseases that need long term / lifelong treatment which is relatively less expensive and benefit has been documented in literature; these diseases need an annual or more frequent monitoring: like those managed by special diet (e.g. Phenylketonuria, galactosemia), or other hormonal and medicinal therapies (e.g. Osteogenesis Imperfecta, Cystic fibrosis, etc.)

Group 3: Diseases for which definitive treatment is existing but it is difficult to make optimal patient selection for benefit, is highly expensive and treatment has to be administered lifelong. Good long term outcomes of the treatment have been seen for some diseases in this group (e.g. Gaucher disease, Pompe Disease, etc.), and for some literature/ scientific data is less or the treatment costs are high (e.g. Duchenne Muscular Dystrophy, Wolman Disease, etc.)

4. Treatment

Despite promising diagnostic advancements, only 5% (about 500 out of 7,000) of the identified RDs, those with known molecular causes, have approved treatments (17,18). Gene therapies have received FDA approval, with numerous others undergoing clinical evaluation. Utilizing adenoviral vectors, a common tool in gene therapy, shows promise in treating various diseases, including hematological disorders, genetic conditions, rare diseases, and tumors (19,20). Some marketed therapies are (21):

- ALLOCORD (HPC, Cord Blood) from SSM Cardinal Glennon Children's Medical Center
- BREYANZI (Lisocabtagene Maraleucel) by Juno Therapeutics, Inc., a Bristol-Myers Squibb Company
- LUXTURNA (Voretigene Neparvovec-Rzyl) developed by Spark Therapeutics, Inc.
- IMLYGIC (Talimogene Laherparepvec) from BioVex, Inc., a subsidiary of Amgen Inc

Stem cells: Hematopoietic stem cell transplantation (HSCT) and white umbilical cord blood stem cells (UCBT) (e.g. used for cytomegalovirus infection); Antibody therapy; Enzyme replacement therapy (e.g. FDA approval of Genzyme's recombinant glucocerebrosidase in 1994) have been the other treatment options (20).

5. Clinical trials for orphan drugs

From the overview of RDs. it is self-explanatory how diverse the diseases and their therapies are. Orphan drug is a drug intended for use in a RD. In the development pathway for a new drug/ therapy, one of the stages is the conduct of clinical trials. The usual pathway includes conduct of Phases 1, 2 and 3 and submitting a New Drug Application. In order to conduct a clinical trial, the study protocol has to be drafted and then approved by the Institutional Ethical committee. The investigators brochure and the informed consent form are integral parts of the protocol along with the details of compensation and other relevant information about the rights of the trial participants. Generating an informed consent form itself would be a challenge when it comes to orphan drugs. Leaving aside financial concern, developing therapies for rare disorders is fraught with challenges. The constraints of small populations magnify these necessities into formidable hurdles (22). For a RD, there is not much validated information available to be provided to the study volunteers and secondly getting participants enrolled is itself a challenge. With more than 50% RD being paediatric, ethical issues pose a concern too to conduct clinical trial. Some more factors are:

- **Trial designs**
  In research settings, the randomized controlled trial is frequently regarded as the benchmark for establishing efficacy but this design is challenging to execute in case of RDs.

- **Patient history and registries**
  Lack of understanding the disease progression hinders identification of key milestones, assessment of crucial disease aspects, inclusion/exclusion criteria, and defining clinically significant differences

- **Subject recruitment and retention**
  Recruiting eligible participants in a timely manner poses a challenge with patients being at different disease stages, different geographic locations and also may have physical impairment to participate in a trial.

- **Drug development and funding**
  Drug development is costly and time-consuming, particularly for rare, fatal paediatric disorders lacking industry funding. Funding agencies prioritize projects with broad public health impact amid economic competition.

- **Training the researchers**
  A shortage of clinical researchers proficient in designing and conducting trials exists when it comes to RDs (22).

- **Choosing study endpoint**
  Endpoint selection is a challenge due to the lack of proper understanding of the RD. Small study sizes call for endpoints with large effect sizes. For diseases impacting multiple organ systems, endpoints evaluating mean change within individuals across multiple parameters may be preferable (23).

6. Regulatory considerations for orphan drug clinical trials

As per USFDA, for an Orphan drug, upon approval, the sponsor benefits by obtaining tax credits for qualified clinical trials, getting exemption from user fees and securing potential 7 years of market exclusivity. 21CFR Part 316 on orphan drug allows a sponsor to provide and investigational drug under a treatment protocol, to those who need it (24). USFDA also supports approvals of orphan drugs based on early phase, nonrandomized, unblinded trial designs with less subjects unlike studies on nonorphan drugs (25). Central Drugs Standard Control Organization (CDSCO) has considered giving a waiver of conducting clinical trials on Indian population for drugs approved outside India if the drug is an orphan drug. CDSCO also provides scope for expedited review for orphan drugs (26). The New Drugs and Clinical Trial Rules 2019 gives a provision that sponsor need not pay any fee for conduct of a clinical trial in the case of orphan drugs.

7. Conclusion

Approved treatment options are desperately needed to treat patients with RDs. The regulatory bodies and policies of various nations across the globe are aligned to facilitate, fund and support clinical development and the approval of drugs to address RDs. Technological advancements too using organ on chip for clinical trials/ AI tools aid in diagnosis and approval of therapy for RDs (27–29). There is tremendous scope for collaborative work in the health care sector to tackle RDs.

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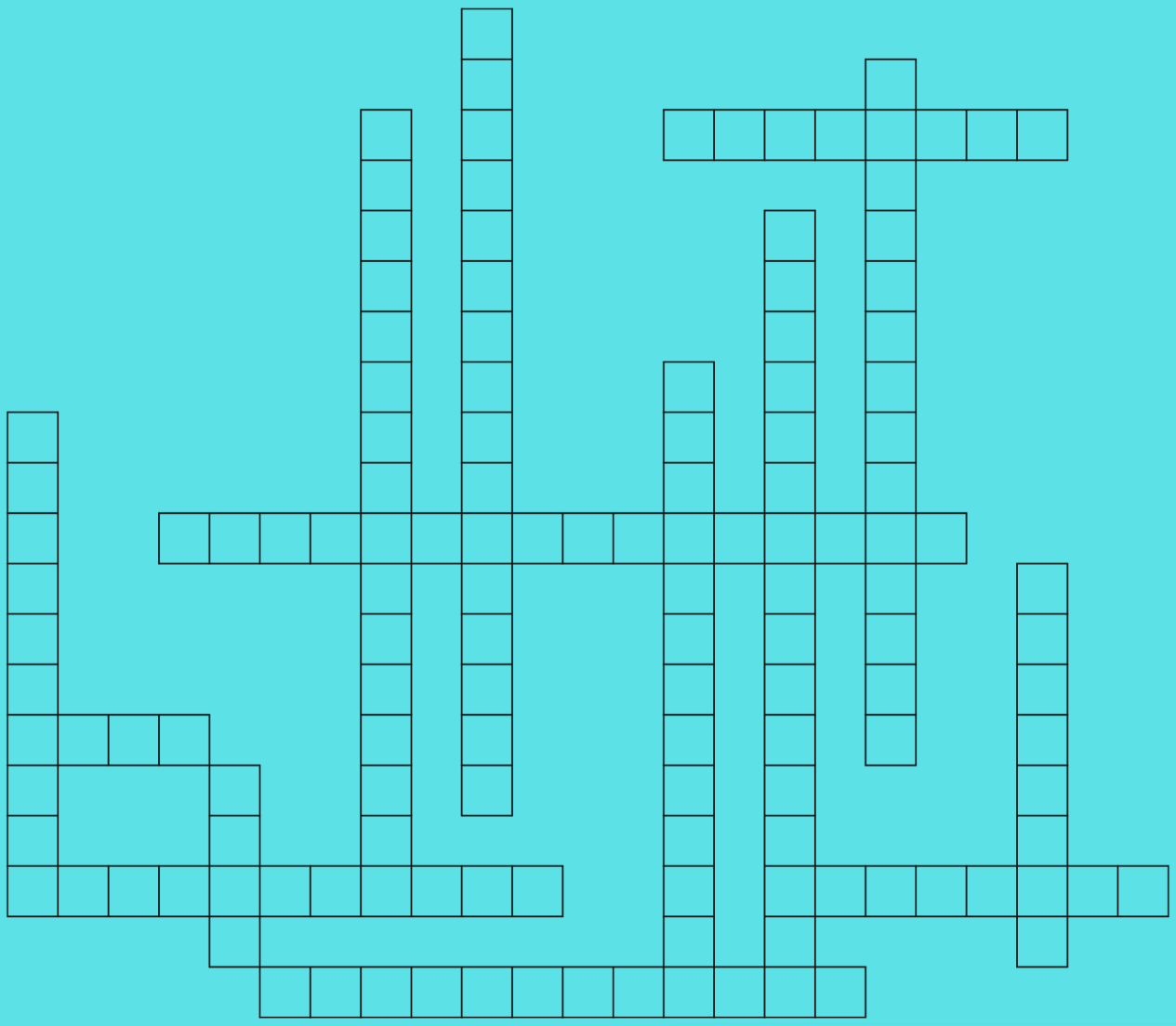
Name:_____

Complete the crossword puzzle below



Across

4. Database of information on rare diseases and orphan drugs for all publics
8. Rare disease associated with adrenal glands
10. Indian Organization for Rare Diseases
12. Rare autoimmune disorder causing abnormal skin thickening
13. Rare skin condition
14. Rare Lysosomal Storage Disease

Down

1. Rare hereditary disorder that causes mental retardation
2. Rare Disease associated with deficiency of glucocerebrosidase enzyme
3. Rare autoimmune disorder involving lymphocyte
5. Rare autoimmune disorder affecting muscles
6. Rare gluten disorder
7. Rare disease involving inflammation of blood vessels
9. Rare aging related disease
11. Group of leading companies committed to helping people with rare diseases

Answers are on page 185

Orphan and rare diseases: Global prevalence in genomic era



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1. Introduction

Orphan and rare diseases present a significant healthcare challenge due to their low occurrence rates, often affecting less than 1 in 2,000 individuals in Europe. The scarcity of these conditions complicates research and treatment efforts, as pharmaceutical companies find it difficult in investment of resources and man power thus resulting in a lack of effective therapies (1).

However, with the advancements in genomics and personalized medicine, new opportunities have emerged for understanding and managing these diseases. Firms such as Orphanet and the National Organization for Rare Disorders (NORD) play vital roles in offering comprehensive support, information, and advocacy for individuals impacted by orphan and rare diseases. Orphanet serves as a European hub for rare disease and orphan drug information, furnishing detailed insights into disease classifications, associated genes, and clinical signs. Conversely, NORD provides a repository of rare disease data, along with avenues for financial and medical aid, as well as resources catering to patients, researchers, and healthcare providers in the world (2).

Both Orphanet and NORD emphasize the significance of raising awareness, conducting research, and extending support to tackle the distinctive challenges posed by orphan and rare diseases. Their collaborative efforts contribute to enhancing the visibility of these conditions within healthcare and research systems, thereby facilitating improved diagnosis, care, and treatment for affected individuals (2, 3).

Table 1. Examples of the orphan and rare diseases (2)

S. No.	Disease name	Onset of age
1.	Abdominal muscle deficiency syndrome	Antenatal, Neonatal
2	Abnormally invasive placenta	NA

3.	Absence of fingerprints-congenital milia syndrome	Childhood
4.	Angora hair nevus	Infancy, Neonatal
5.	Autoimmune hemolytic anemia	All ages
6.	Bacterial endocarditis	All ages
7.	Benign adult familial myoclonic epilepsy	All ages
8.	Bloom syndrome	Antenatal, Neonatal
9.	Body stalk anomaly	Infancy, Neonatal
10.	Bone necrosis	NA
11.	Cancer of penis	Elderly
12.	Carcinoma of vulva	NA
13.	Cardiogenital syndrome	Infancy, Neonatal
14.	Central core disease	Childhood
15	Dancing eye-dancing feet syndrome	Childhood, Infancy
16.	Deep dermatophytosis	Adult, Childhood
17.	Dermal sinus tract	NA
18.	Disorder of sex development	NA
19.	Eating reflex epilepsy	NA

20.	Embryonal sarcoma of the liver	NA
21.	Enlarged parietal foramina	Antenatal, Neonatal
22.	Epidermal nevus syndrome	Infancy, Neonatal
23.	Familial amyloid nephropathy	All ages
24.	Familial joint instability syndrome	Adolescent, Childhood, Infancy
25.	Farmer's lung disease	NA
26.	Female infertility due to zona pellucida defect	Adult
27.	Generalized fetal edema	Antenatal
28.	Genetic gastro-esophageal disease	NA
29.	Genetic respiratory malformation	NA
30.	Hendra virus infection	All ages
31.	Hepatitis delta	All ages
32.	Hereditary gingival fibromatosis	All ages
33.	Idiopathic achalasia	All ages
34.	Immunoglobulin A nephropathy	NA
35.	Infantile spasms syndrome	Childhood, Infancy, Neonatal

36.	Juvenile polyarthritis	NA
37.	Jackson-Barr syndrome	NA
38.	Kosaki overgrowth syndrome	Infancy
39.	Kuskokwim syndrome	Childhood, Neonatal
40.	Kyasanur forest disease	All ages
41.	Lassa fever	All ages
42.	Lateral facial cleft	Antenatal, Neonatal
43.	Late-onset retinal degeneration	Adult, Elderly
44.	Lactotroph adenoma	Adolescent, Adult, Childhood, Elderly
45.	Localized pagetoid reticulosis	Adult
46.	Macrodactyly of hand, bilateral	NA
47.	Multiple acyl-CoA dehydrogenase deficiency	All ages
48.	Malformation of the cerebellar vermis	NA
49.	Male-limited precocious puberty	Childhood
50.	Mast syndrome	Adolescent, Adult, Childhood
51.	Nail anomaly	NA

52.	Nanophthalmos	Infancy, Neonatal
53.	Nasal dermoid cyst	NA
54..	Necrotizing enterocolitis	Neonatal
55.	Neurogenic sarcoma	Adolescent, Adult, Childhood, Elderly, Infancy
56.	Obesity due to congenital leptin deficiency	Childhood
57.	Hepatoportal sclerosis	All ages
58.	Oculocutaneous albinism	Neonatal
59.	Occupational allergic alveolitis	NA
60.	Oculoskeletodental syndrome	Adolescent, Adult, Childhood
61.	Oculodentodigital dysplasia	Infancy, Neonatal
62.	Oral submucous fibrosis	All ages
63.	Paget disease of the nipple	Adult
64.	Pulmonary arterial hypertension	All ages
65.	Pulmonary arterial hypertension associated with HIV infection	Adult
66.	Pancreatic cholera	All ages
67.	Papular mucinosis of infancy	NA

68.	Arterial duct anomaly	NA
69.	Periodic paralysis	NA
70.	Peruvian warts	NA
71.	Query fever	All ages
72.	defects of plectin	NA
73.	Question mark ear syndrome	Infancy, Neonatal
74.	Quantal squander syndrome	All ages
75.	defects of myofibrillar proteins	NA
76.	Radioulnar fusion	Childhood, Infancy
77.	Rajab-Spranger syndrome	Childhood
78.	Renin-angiotensin-aldosterone system-blocker-induced angioedema	Adult
79.	Rabies	All ages
80.	Riboflavin transporter deficiency	Adolescent,Adult Childhood, Infancy
81.	Ring chromosome 1 syndrome	Neonatal
82.	Renal nutcracker syndrome	Adult
83.	Russell-Weaver-Bull syndrome	Antenatal

84.	Salla disease	Infancy
85.	Salivary gland type cancer of the breast	Adult
86.	Sarcosinemia	All ages
87.	Transaldolase deficiency	Infancy, Neonatal
88.	Tropical pancreatitis	Childhood
89.	Teratogenic Pierre Robin syndrome	NA
90.	Unbalanced complete atrioventricular canal	NA
91.	Univentricular cardiopathy	NA
92.	Uveal melanoma	Adult
93.	Vulvar carcinoma	NA
94.	Vaginal atresia	Childhood
95.	Valley fever	All ages
96.	Vascular tumor with associated anomalies	NA
97.	Vitamin D dependent rickets type I	Infancy, Neonatal
98.	Vanishing testes syndrome	Neonatal
99	Zika virus disease	All ages
100.	Zimmermann-Laband syndrome	Neonatal

2. Absence of fingerprints or congenital Milia syndrome

Congenital Milia disorder is a very uncommon hereditary disease that is distinguished by a unique set of symptoms. These symptoms include the absence of fingerprints on the hands and feet, the presence of blisters in new born, and the development of small white papules called milia, particularly on the face. This syndrome has been observed in two families, one of which has had members affected for three generations, totalling 13 individuals. Additionally, there is an unrelated person who also shows similar symptoms. Some individuals with this syndrome may also experience certain physical abnormalities, such as partial flexion contractures in their fingers and toes, as well as webbing between their toes. Some of the clinical features of the disease may include:

- Permanent finger flexion (camptodactyly)
- Skin rash
- Abnormal blistering
- Variations in skin thickness
- Reduced sweating (hypohidrosis)
- Unusual fingerprints
- Milia
- Amniotic constriction ring

However, the exact onset of these features remains unclear. Mutations in the SMARCAD1 gene are linked to this syndrome, which follows an autosomal dominant inheritance pattern (4,5).

2.1 Prevalence of congenital Milia syndrome

The prevalence of Congenital Milia Syndrome, specifically the variant characterized by the absence of fingerprints, is extremely rare. Only about 10 families worldwide have been identified as affected by this disorder, indicating its rarity and the limited understanding of its incidence in the general population (5).

3. Query fever or infection due to *Coxiellaburnetii*

Q fever, also known as query fever, a widespread transmittable disease caused by a bacterium called *Coxiellaburnetii*. It is caused by both humans and animals. The name "Q" was chosen because the origin of the disease was initially uncertain. This condition primarily affects cattle, sheep, and goats, and humans usually contract it by inhaling dust that is contaminated by these animals. People at higher possibility of getting Q fever cover those who work in farming, veterinary, or have close contact with these animals. The symptoms of Q fever can vary from mild flu-like symptoms to cases with no symptoms at all. However, in severe cases, it can lead to chronic infections that affect important organs such as the heart, liver, lungs, and brain. This is particularly true for individuals with pre-existing heart valve issues or weakened immune systems. To diagnose Q fever, blood antibody tests are typically performed, and the treatment approach depends on the severity of the symptoms. Antibiotics are effective for severe or chronic cases. Preventive measures include disinfecting areas contaminated by the bacterium and maintaining thorough hand hygiene to minimize the risk of infection (6,7).

Some of the clinical features that may be observed in individuals with Q fever are as follows (6-9):

- **Fever:** One of the most commonly recognized symptoms is a high-grade fever (104°F or 40°C).
- **Flu-like symptoms:** Common flu-like symptoms include chills, sweats, fatigue, headache, soreness, nausea, vomiting, loss motion, and a dry cough.
- **Chest and abdominal pain:** Chest pain while breathing and abdominal pain can occur.
- **Pneumonia and hepatitis:** In severe cases, Q fever can lead to lung infection (pneumonia) or liver infection (hepatitis).

- **Chronic complications:** A small percentage (less than 5%) of infected individuals may form over a long time Q fever, which causes endocarditis and may cause symptoms like night sweats, fatigue, shortness of breath, weight loss, and swelling of the limbs.
- **Pregnancy complications:** Women infected with Q fever in pregnancy can be at risk of miscarriage, stillbirth, premature delivery, or giving birth to a low-weight just birth child.

3.1 Prevalence of query fever syndrome

The estimated regularity of Q fever in human serum samples in the Eastern Mediterranean region is 25.5%, with a wide range of 16.1% to 34.9% based on different studies. Specifically, studies conducted in Afghanistan found a prevalence rate of 34.4%, also with high variability (ranging from 0.0% to 76.8%). Other countries in the region such as Egypt, Iran, Iraq, Jordan, Lebanon, Oman, Pakistan, Saudi Arabia, Somalia, Sudan, Tunisia, and the United Arab Emirates had prevalence rates ranging from 15.8% to 59.1%, showing varying levels of heterogeneity. Overall, the popularity of Q fever in the Eastern Mediterranean region was reported to be 22.4% among humans, animal species, mites and ticks, and milk samples. These findings emphasize the significant presence of this fever in the region, especially among high-risk occupational groups and populations exposed to livestock (10).

4. Carcinoma of valva

Vulvar cancer, also known as carcinoma of the vulva, is a relatively uncommon type of cancer affecting the outer region of the female genitalia. Most cases, about 90%, are squamous cell carcinomas, originating from the thin, flat squamous cells that line the vulva. These cancers can develop from precancerous conditions like vulvar intraepithelial neoplasia (VIN), where untreated abnormal cell changes may progress to cancer. Risk factors for this infection is smoking, and certain skin conditions such as lichen sclerosus.

Typical symptoms of vulvar carcinoma include itching, burning, soreness, lumps, swelling, wart-like growths, changes in skin texture, and unusual discharge from vulvar lesions. Diagnosis usually entails a physical examination, colposcopy, and biopsy to confirm the presence of cancerous cells.

Treatment for vulvar carcinoma may include surgery, radiation therapy, chemotherapy, and immunotherapy, tailored to the cancer's stage and the individual patient's needs. Early detection and prompt treatment are crucial for effectively managing vulvar carcinoma and improving outcomes for those affected (11-13).

Some of the clinical features of the disease may include (13,14):

- **Itching:** It is the most frequent and persistent indication of vulvar cancer.
- **Bleeding, discharge, and pain:** Other common symptoms include bleeding, unusual discharge, painful urination, and pain.
- **Lump or mass:** The most noticeable sign of vulvar cancer is a lump or mass in the vulva, which may appear ulcerated, white, fleshy, or wart-like.
- **Skin changes:** Swollen lumps in the vulva that may be red, white, or dark brown can be a symptom.
- **Lymph node swelling:** Swollen or tender lymph nodes in the groin area can also indicate vulvar cancer.
- **Precancerous conditions:** Vulvar intraepithelial neoplasia (VIN), a precancerous condition, is a risk factor and can precede the development of vulvar cancer

4.1 Prevalence of carcinoma of vulva

Vulvar cancer is not very common, with about 2.5 cases per ten thousand women each year in the USA. The rates of this cancer and the number of deaths it causes vary a lot depending on a person's ethnicity. Non-Latino white women have the elevated rates of vulvar cancer compared to other groups of people (13).

5. Vanishing testes syndrome

Vanishing testes syndrome, or testicular regression syndrome (TRS), is a rare condition where a testis undergoes atrophy and disappears during foetal development. It's believed to stem from events like intrauterine or perinatal testicular torsion, vascular blockage, or hormonal imbalances. Key signs include the absence of a detectable testis during a physical exam, resulting in an apparently "empty" scrotum, and the presence of a closed-off spermatic cord, indicating early testicular formation. Biopsy often shows a fibrovascular nodule with specific cell types and calcification, with few cases retaining any testicular tissue. While there's a theoretical risk of cancer, no instances have been documented. TRS occurs in about 5% of cryptorchidism cases and makes up a significant portion of nonpalpable testis situations, surpassing complete testicular absence in this group (15-17).

5.1. Prevalence of vanishing testes

While vanishing testes syndrome is a relatively uncommon condition, it accounts for a significant proportion of cases with a nonpalpable testis, estimated to affect up to 1 in 1,250 males (18).

6. Alice in wonderland syndrome

Alice in Wonderland Syndrome (AIWS) is a odd neurological condition that causes deformation in how individuals perceive themselves and their surroundings. This can include seeing objects as larger or smaller than they really are, as well as feeling like their own body size has changed. The condition, titled after Lewis Carroll's "Alice's Adventures in Wonderland," is not contagious and mostly affects children and teenagers, but it can occur at any age. AIWS is often linked to migraines, infections like Epstein-Barr virus (EBV) and influenza, as well as seizures, strokes, mental health conditions, and certain medications or drugs. Despite its rarity, AIWS is estimated to affect up to 30% of teenagers, showing that it's more common in certain groups.

Symptoms of AIWS can be grouped into disturbances in how individuals perceive themselves, how they see things, or a combination of both. Self-perception disturbances involve altered perceptions of body size and shape, while visual perception disturbances affect how objects and spaces are viewed. These symptoms can be distressing and confusing, so accurate diagnosis and treatment are important.

Treating AIWS involves addressing the underlying causes, as there's no direct cure for the syndrome itself. This may include managing migraines, treating infections, controlling seizures, or adjusting medications. In some cases, reassurance alone may be enough, especially if symptoms are temporary and not causing significant distress. However, effectively managing chronic conditions like migraines or epilepsy may decrease the frequency and severity of AIWS symptoms (19,20).

7. Conclusion

In conclusion, the landscape of orphan and rare diseases presents a complex healthcare challenge due to their low occurrence rates and the resulting difficulties in research and treatment efforts. However, with the advent of genomics and personalized medicine, new avenues have emerged for understanding and managing these conditions. Organizations like Orphanet and NORD play pivotal roles in offering comprehensive support, information, and advocacy for individuals impacted by orphan and rare diseases. By emphasizing the importance of raising awareness, conducting research, and extending support, these organizations contribute significantly to improving the visibility of these conditions within healthcare and research systems. Ultimately, collaborative efforts in the field of orphan and rare diseases are essential for enhancing diagnosis, care, and treatment outcomes for affected individuals worldwide.

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A rare disease: Sleep paralysis

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Abstract

A confusing phenomenon that arises in the transitional state between waking and sleep is sleep paralysis. It causes a transient paralysis in which people are fully cognizant but confined to their bodies, unable to move or communicate. Numerous vivid hallucinations, from visual disruptions to unsettling audio and tactile experiences, frequently accompany this emotion. Though its exact causes are still unknown, sleep paralysis is known to be strongly connected to disturbances in the regular sleep cycle, especially during REM sleep, which is the stage of sleep connected to vivid dreams. Numerous factors contribute to the onset of sleep paralysis, including irregular sleep patterns, sleep deprivation, stress, and certain sleep disorders like narcolepsy.

Keywords: Sleep paralysis, REM sleep, Psychological impact, Anxiety, Hallucinations.

1. Introduction

Sleep paralysis is the temporary immobility or inability to speak or move during the process of falling or staying asleep. People may also hallucinate during sleep paralysis (1). It usually happens when the phases of alertness and sleep are changing, especially during rapid eye movement (REM) sleep. Although the precise origin of sleep paralysis is unknown, disturbed REM sleep patterns are thought to be a contributing factor (2). To prevent acting out dreams, the body's muscles are effectively immobilized while the brain is intensely engaged during REM sleep. When someone has sleep paralysis, they experience a brief period of paralysis following awakening, which makes them feel immobile (3). Sleep paralysis-related hallucinations are believed to result from the brain's attempt to interpret the strange event. Due to its short duration (a few minutes to several minutes), intense hallucinations, and sensations of chest pressure or suffocation, previous researchers have compared SP to nightmares., a few things can make it more likely to happen, such as (2, 4):

- Inadequate sleep or irregular sleep patterns
- Lack of sleep
- Anxiety and stress
- Mental health issues including anxiety attacks or depression

1.1 Ancient background

Traditionally, SP was described as "not a bad dream," but rather as the nighttime visitation of a malevolent entity that threatened to rip the life from its scared victim, hundreds of years ago. Those who had Sleep Paralysis reported feeling immobilized, speechless, helpless, and overcome by overwhelming anxiety and terror (2). Between 1.7% and 40% of the general population are believed to be impacted by sleep paralysis, with students making up the ultimate of those affected (4,5). It usually peaks at thirty years of age and seems to be linked to panic episodes, narcolepsy, and posttraumatic stress disorder (PTSD) (6). Similarly, there is evidence to suggest that sleep paralysis, bipolar disorder, and schizophrenia are related (7). The phrase "sleep paralysis" has been used for many different purposes since it was first used more than hundreds of years ago (8,9).

1.2 Epidemiology

Though lifetime incidence of sleep paralysis in the overall population has been estimated by metanalytic evaluations to be around 8%, it is an uncommon condition. It's noteworthy to observe, though, the fact that the prevalence varies greatly amongst individual research, with values ranging from 2% to 60% (10,11). It is critical to remember that several factors contribute to the diversity in prevalence, the two most significant of which are the disparities in the terminology and the various scales used for assessment (12). Globally, there are no appreciable differences between the genders within the documented experiences of sleep paralysis (Studies have found a few minor variations, with some reporting that sleep paralysis is more common in men and others in women) (13).

2. Types of sleep paralysis

Most instances of paralysis during sleep are divided into two categories by medical professionals.

2.1 Isolated sleep paralysis (ISP)

These isolated episodes of paralysis are not associated with an underlying diagnosis of narcolepsy, a neurological disorder that usually causes sleep paralysis and affects the brain's capacity to control attentiveness. Narcolepsy and recurrent sleep paralysis are linked (14,15).

2.2 Recurrent isolated sleep paralysis (RISP)

This is a condition that involves recurring episodes of sleep paralysis in an individual who does not have narcolepsy (16)

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3. Contributing factors to sleep paralysis

The following are the determinants impacting sleep paralysis:

3.1 Factors related to the population

Even though anyone regardless of age can get sleep paralysis, it often affects teenagers and young adults more frequently (17). According to certain research, women may be marginally more prone than men to get sleep paralysis (18).

3.2 Correlation with sleep disorders

Narcolepsy, obstructive sleep apnea, insomnia, and sleep paralysis are frequently accompanied by different sleep disorders (19).

3.3 Anxiety and depression

It has been determined that stress and mental health disorders like these may be risk factors for sleep paralysis (10,15).

3.4 Consequence on life quality

Fear, anxiety, and trouble sleeping can all be brought on by sleep paralysis, which could significantly impair someone's quality of life (1,4).

3.5 Hereditary factors

A potential hereditary component has been suggested by family studies that have shown an increased incidence of sleep paralysis among afflicted persons' relatives (20).

4. Neurophysiology

The regular sleep-wake cycle and the transition between distinct stages of sleep are thought to be disrupted in cases of sleep paralysis, according to neurophysiology (21). To keep people from acting out their dreams, the body typically experiences muscular atonia, or momentary paralysis, during REM sleep, which is the period of sleep linked to vivid dreams (22). The sense of being immobile occurs when this muscular atrophy in sleep paralysis continues into consciousness. Studies on the brainstem and neurotransmitters, especially those involving serotonin and gamma-aminobutyric acid (GABA), indicate that anomalies in these processes may have a role in the development of sleep paralysis (23,24).

5. Clinical manifestation of sleep paralysis

Atonia is the characteristic indication of sleep paralysis, characterized by a failure to move or speak. (25). People also report breathing problems, Pressure on the chest, Rapid Heart Beat, and uncomfortable emotions like fear or helplessness during periods of sleep paralysis (26). These can manifest as hypnopompic hallucinations upon waking up or as hypnagogic hallucinations throughout sleep (27). Figure 1 illustrates the symptoms of sleep paralysis.

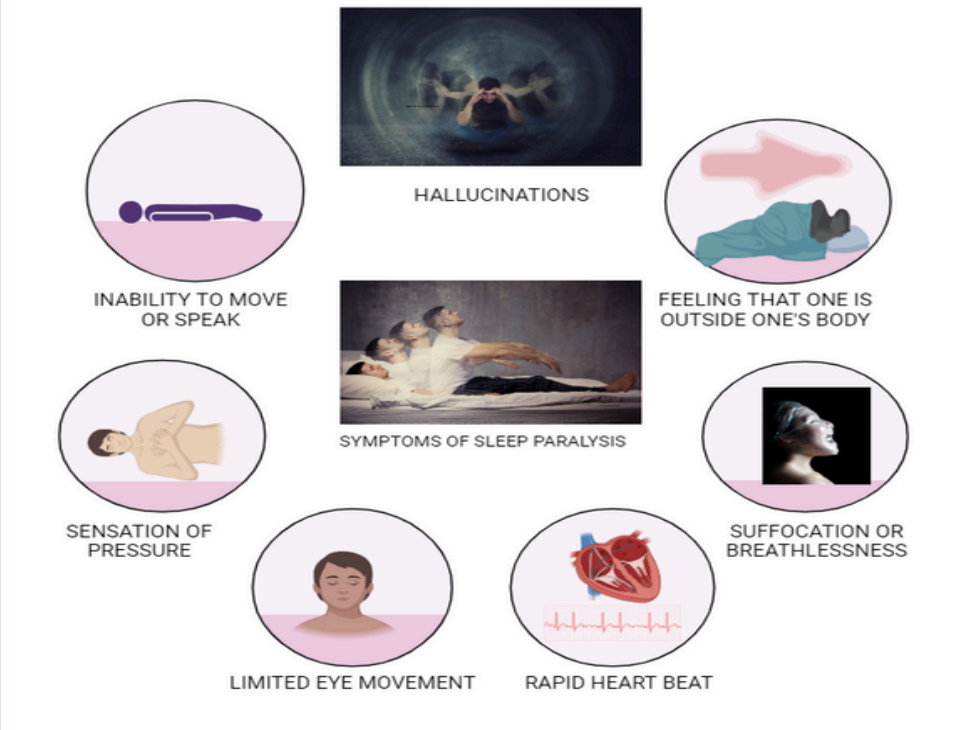

Figure 1. Symptoms of sleep paralysis

When sleep paralyzed, hallucinations usually fall into one of three categories:

5.1 Hallucinations of intruders

These entail sensing that there is a dangerous or evil person or thing present in the space (28).

5.2 Incubus hallucinations

Victim experiences breathing difficulties or a sensation of something pushing down on their chest (29).

5.3. Vestibular-motor hallucinations

Movement or floating sensations, as if one were being lifted off the bed or dragged around the room, are characteristic of vestibular-motor hallucinations (30).

6. Management of sleep paralysis (31)

Since sleep paralysis frequently happens only once,, medical or mental health specialists may not be necessary in many circumstances. But the following conditions need to get expert assistance:

- In cases where sleep paralysis occurs frequently.
- When it is hard to fall asleep every day.
- Excessive worry about going to sleep.
- Narcolepsy symptoms.

It can be managed in following ways:

- **By maintaining sleep hygiene**: Creating a comfortable, adhering to regular sleep patterns, obtaining 6 to 8 hours of sleep, and using appropriate sleep hygiene. By altering the sleeping environment, Sleep paralysis may be avoided by abstaining from large meals, smoking, and consuming coffee or alcohol soon before bed (32).

- **Psychotherapy**: Patients with sleep paralysis may benefit from psychotherapy, particularly if they are suffering anxiety, fear, or distress because of their experiences. Cognitive-behavioural therapy (CBT) is one therapeutic strategy that can do this (33).

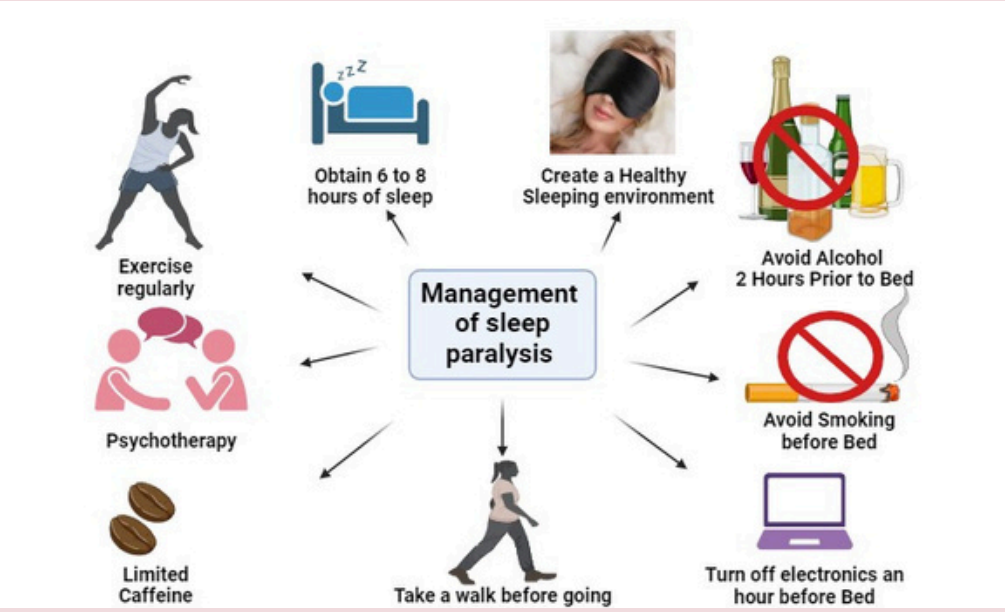

Figure 2. Management of sleep paralysis

7. Conclusion

The scientific understanding of sleep paralysis and its validation as a rather normal sleep condition remain unchanged. Research into the history, risk factors, and effects of sleep paralysis on people's well-being is being conducted in the fields of sleep medicine, psychology, and neuroscience. Treatment attempts usually emphasize on reducing the anxiety associated with this experience by teaching people about the nature of sleep paralysis, controlling stress, and the underlying sleep illnesses. The basic features and prevalence of sleep paralysis have not changed over time, even though some of our pioneers in its study and treatment may still be considered pioneers.

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Narcolepsy rare disease: Symptoms, causes, and management

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Abstract
Narcolepsy, a chronic neurological disorder, disrupts the sleep-wake cycles of the brain, leading to debilitating symptoms such as excessive daytime sleepiness, cataplexy, hallucinations, and sleep paralysis. This article explores the symptoms, causes, diagnosis, and management of narcolepsy. Key aspects include genetic predisposition, neurotransmitter imbalances, autoimmune dysfunction, and environmental triggers as contributing factors. Diagnosis involves clinical assessment and objective sleep studies, while management encompasses medication, lifestyle modifications, and supportive therapies. Coping strategies emphasize education, communication, and self-care practices. Increased awareness and research are crucial for improving outcomes and fostering a supportive environment for individuals living with narcolepsy.

Keywords: Narcolepsy, Excessive daytime sleepiness, Cataplexy, Sleep paralysis diagnosis and management

1. Introduction

Narcolepsy, a chronic neurological disorder, intricately disrupts the delicate balance of the sleep-wake cycles of the brain, profoundly impacting the daily functioning of an individual. Characterized by an array of symptoms, including excessive daytime sleepiness, sudden and involuntary loss of muscle tone known as cataplexy, hallucinations, and episodes of sleep paralysis, narcolepsy presents formidable challenges to those affected and their families (1,2). Despite its debilitating nature, narcolepsy frequently evades detection or is misdiagnosed, further complicating the journey for patients as they navigate its complex manifestations (3). This underlines the pressing need for heightened awareness, accurate diagnosis, and effective management strategies to alleviate the burdens imposed by this enigmatic condition (4).

2. Symptoms of narcolepsy

Symptoms of narcolepsy include excessive daytime sleepiness, sudden loss of muscle tone (cataplexy), hallucinations, and sleep paralysis, profoundly impacting daily functioning and quality of life. Recognition of these hallmark symptoms is vital for accurate diagnosis and timely intervention (5,6).

2.1. Excessive daytime sleepiness

Individuals with narcolepsy experience overwhelming daytime drowsiness, often leading to sudden and uncontrollable sleep attacks.

2.2 Cataplexy
Sudden episodes of muscle weakness or paralysis triggered by strong emotions such as laughter, excitement, or anger (5).pressing need for heightened awareness, accurate diagnosis, and effective management strategies to alleviate the burdens imposed by this enigmatic condition (4).

2.3 Hallucinations
Vivid and often frightening hallucinations that occur when falling asleep or waking up.

2.4 Sleep paralysis
Temporary inability to move or speak while falling asleep or waking up, often accompanied by hallucinations (5,6).

3. Causes and risk factors
The causes and risk factors of narcolepsy are multifaceted, encompassing genetic predisposition, neurotransmitter imbalances, and potential autoimmune dysfunction, alongside environmental triggers. Understanding these interrelated factors is crucial in unravelling the complexities of narcolepsy and guiding effective management strategies (7,8).

3.1 Genetic predisposition
Narcolepsy often trace back to familial ties, with a notable genetic predisposition. Research has identified specific gene variants associated with an increased risk of developing the disorder. These genetic markers can be passed down through generations, predisposing certain individuals to narcolepsy. However, the interplay between genetics and environmental factors remains a subject of ongoing investigation (7).

3.2 Neurotransmitter imbalance
Central to understanding narcolepsy is the disruption in hypocretin production, a crucial neurotransmitter that governs wakefulness and rapid eye movement (REM) sleep. This neurotransmitter, also known as orexin, is synthesized by neurons in the hypothalamus. In individuals with narcolepsy, there is often a deficiency in hypocretin levels or impaired functioning of hypocretin receptors, leading to dysregulation of sleep-wake cycles. The exact mechanisms underlying this imbalance are complex and multifaceted, involving intricate interactions within the neural networks of the brain (8).

3.3 Autoimmune dysfunction
Emerging evidence suggests that autoimmune dysfunction may contribute to the pathogenesis of narcolepsy in certain cases. In autoimmune narcolepsy, the immune system of the body erroneously targets and destroys the cells responsible for producing hypocretin. This autoimmune attack leads to a reduction or complete depletion of hypocretin levels in the brain, precipitating the onset of narcoleptic symptoms. The triggers initiating this autoimmune response are still under investigation, with hypotheses ranging from viral infections to environmental exposures (7,8).

3.4 Environmental triggers
While genetic and neurobiological factors lay the groundwork for narcolepsy, environmental triggers can act as catalysts, precipitating or exacerbating symptoms. Stress, trauma, and significant life events are among the myriad environmental factors implicated in triggering narcoleptic episodes. Stress, in particular, can disrupt the delicate balance of neurotransmitters involved in sleep regulation, potentially exacerbating symptoms in susceptible individuals. Furthermore, hormonal changes, such as those occurring during puberty or menopause, may also influence the onset or progression of narcolepsy symptoms, highlighting the intricate interplay between biological and environmental factors in shaping the trajectory of the disorder (7,8).

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4. Diagnosis and evaluation

Diagnosis and evaluation of narcolepsy involve comprehensive clinical assessment, including inquiry into sleep patterns and symptoms, followed by objective sleep studies such as polysomnography (PSG) and multiple sleep latency test (MSLT), to confirm diagnosis and guide treatment decisions (9,10).

4.1 Clinical assessment

The diagnostic journey of narcolepsy begins with a thorough clinical assessment conducted by a healthcare professional specializing in sleep disorders. This assessment involves a detailed inquiry into the medical history of the patient, including their sleep patterns, daytime symptoms, and any relevant familial predispositions. Patients are often asked to provide a comprehensive account of their sleep habits, including the frequency and duration of daytime naps, instances of sudden muscle weakness or collapse (cataplexy), hallucinations, and experiences of sleep paralysis. Additionally, clinicians may inquire about the presence of any comorbid conditions or medications that could potentially influence sleep-wake cycles (9,10).

4.2 Polysomnography (PSG)

Polysomnography, often referred to as an overnight sleep study, serves as a cornerstone in the diagnostic workup of narcolepsy. During this non-invasive procedure, patients spend a night in a sleep laboratory where their physiological parameters are meticulously monitored. This includes recording brain activity (electroencephalogram, EEG), eye movements (electrooculogram, EOG), muscle tone (electromyogram, EMG), heart rate, and respiratory patterns. PSG enables clinicians to identify characteristic abnormalities in sleep architecture, such as shortened REM sleep latency and fragmented sleep patterns, which are indicative of narcolepsy (7-9).

4.3 Multiple sleep latency test (MSLT)

The MSLT complements PSG by assessing daytime sleep propensity and the presence of rapid eye movement (REM) sleep during daytime naps. Following an overnight PSG, patients are subjected to a series of scheduled naps throughout the day in a controlled environment. The MSLT measures the time it takes for individuals to fall asleep during these nap opportunities, known as sleep latency, as well as the presence and timing of REM sleep. In narcolepsy, individuals typically exhibit abnormally short sleep latencies and frequently enter REM sleep during these daytime naps, reflecting the hallmark symptoms of excessive daytime sleepiness and rapid transitions into REM sleep characteristic of the disorder (7-10).

These diagnostic modalities, when used in conjunction with a comprehensive clinical assessment, facilitate the accurate identification and characterization of narcolepsy, enabling healthcare providers to tailor appropriate management strategies to address the unique needs of affected individuals (9,10).

5. Treatment and management

Treatment and management of narcolepsy encompass a combination of medication, such as stimulants and sodium oxybate, lifestyle modifications, including sleep hygiene and strategic napping, and supportive therapies like cognitive-behavioural therapy (CBT) and participation in support groups, aimed at symptom control and enhancing overall well-being (11,12).

5.1 Medications

Stimulant medications, such as modafinil and armodafinil, are commonly prescribed to address the excessive daytime sleepiness characteristic of narcolepsy. These medications work by promoting wakefulness and improving alertness, thereby helping individuals with narcolepsy maintain functional levels of wakefulness throughout the day. They are often considered first-line pharmacotherapy due to their efficacy and relatively low risk of abuse or dependence compared to traditional stimulants. Additionally, other medications such as methylphenidate and amphetamines may be prescribed in cases where modafinil or armodafinil are ineffective or poorly tolerated (11,12).

5.2 Sodium oxybate

Sodium oxybate, also known as gamma-hydroxybutyrate (GHB), is a central nervous system depressant that serves as a cornerstone in the management of narcolepsy, particularly for individuals experiencing cataplexy. This medication is typically administered in divided doses at bedtime and during the night to improve nocturnal sleep quality and reduce the frequency and severity of cataplexy episodes. Sodium oxybate's mechanism of action involves enhancing slow-wave sleep and consolidating sleep architecture, thereby addressing both nocturnal symptoms and daytime manifestations of narcolepsy.

5.3 Lifestyle modifications

In addition to pharmacotherapy, lifestyle modifications play a pivotal role in managing narcolepsy symptoms and optimizing overall well-being. Establishing a regular sleep schedule, maintaining a conducive sleep environment, and practicing good sleep hygiene are essential components of narcolepsy management. Taking short, strategic naps throughout the day can help alleviate daytime sleepiness and prevent the accumulation of sleep debt. Furthermore, avoiding stimulants like caffeine and alcohol, particularly close to bedtime, can minimize disruptions to sleep continuity and promote restorative sleep.

5.4 Supportive therapies

Coping with the challenges of narcolepsy often necessitates psychological and emotional support. Cognitive-behavioural therapy (CBT) can equip individuals with narcolepsy with practical strategies for managing symptoms, addressing sleep disturbances, and coping with psychosocial stressors. Support groups and peer networks provide invaluable emotional support, fostering a sense of community and solidarity among individuals facing similar challenges. These supportive interventions not only enhance coping skills but also empower individuals to proactively manage their condition and improve their quality of life (11,12).

By integrating pharmacotherapy, lifestyle modifications, and supportive interventions, individuals with narcolepsy can effectively manage their symptoms, mitigate the impact of the disorder on daily functioning, and achieve optimal quality of life. Close collaboration between healthcare providers, patients, and their support networks is essential in developing individualized treatment plans tailored to the unique needs and preferences of each individual with narcolepsy (11,12).

6. Coping with narcolepsy

Coping with narcolepsy involves educating oneself about the disorder, fostering open communication with healthcare providers and loved ones, and prioritizing self-care practices to manage symptoms and improve quality of life (13,14).

6.1 Education and awareness

Knowledge is a powerful tool in coping with narcolepsy. Learning about the nature of the disorder, its symptoms, triggers, and available treatment options empowers individuals to make informed decisions about their health. Understanding how narcolepsy impacts daily life allows individuals to recognize and validate their experiences, reducing feelings of isolation and stigma. Educational resources, support groups, and online communities provide valuable insights and perspectives, fostering a sense of connection and solidarity among individuals living with narcolepsy.

6.2 Communication

Effective communication is essential in navigating the challenges of narcolepsy and accessing the support and accommodations needed to manage the condition effectively. Openly discussing narcolepsy with healthcare providers facilitates collaborative decision-making

regarding treatment options, symptom management strategies, and ongoing care. Similarly, transparent communication with employers, colleagues, and educators about narcolepsy-related challenges and needs can help facilitate reasonable accommodations in the workplace or academic settings. Furthermore, maintaining open lines of communication with loved ones fosters understanding, empathy, and a supportive environment conducive to managing narcolepsy-related difficulties (13).

6.3 Self-care

Prioritizing self-care is crucial for individuals living with narcolepsy to optimize their physical and emotional well-being. Engaging in regular exercise not only improves overall health but also promotes better sleep quality and daytime alertness. Stress management techniques, such as mindfulness meditation, deep breathing exercises, or relaxation techniques, can help alleviate anxiety and minimize the impact of stress-related triggers on narcolepsy symptoms. Additionally, adopting healthy eating habits, including a balanced diet rich in nutrients and avoiding excessive consumption of stimulants like caffeine, supports stable energy levels and promotes better sleep hygiene. By incorporating self-care practices into their daily routine, individuals with narcolepsy can enhance their resilience, manage symptoms more effectively, and improve their quality of life (13,14).

Coping with narcolepsy requires a multifaceted approach that encompasses education, communication, and self-care. By proactively seeking knowledge, fostering open communication with healthcare providers and support networks, and prioritizing self-care activities, individuals with narcolepsy can navigate the challenges posed by the disorder with resilience, empowerment, and a sense of agency (13,14).

7. Conclusion

Narcolepsy is a challenging disorder often misunderstood, yet with proper diagnosis, treatment, and support, individuals can effectively manage symptoms and lead fulfilling lives. Increased awareness, advocacy, and research are crucial in improving outcomes for those affected by narcolepsy. Through education, open communication, and ongoing advancements, individuals with narcolepsy can navigate the complexities of the condition with resilience and hope, paving the way for a more supportive and inclusive future.

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Unveiling and understanding omphalitis: An obscure orphan disease in new-borns



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Abstract

Omphalitis is a serious infection of the umbilical cord stump, often caused by Staphylococcus aureus and other bacteria, leading to complications such as necrotizing fasciitis. This review highlights the etiology, and diagnostic approaches associated with omphalitis, with a particular focus on Staphylococcus aureus infections. Clinical cases from different countries illustrate variability in management of omphalitis. Additionally, insights into the potential use of umbilical cord blood stem cells as a future therapeutic approach are discussed, suggesting approach for personalized medicine.

Keywords: omphalitis, umbilical cord, bacteria, infants, clinical trial

1. Introduction

The umbilical cord is a tube-like structure that joins the newborn to the placenta of the mother (1). There are two methods for clamping the foetal cord: the standard (traditional method) and the delay clamping method. This procedure is performed within 30 to 60 seconds after birth. There are more benefits of delayed clamping. This reduces the risk of postpartum hemorrhage, enhances iron circulation, increases red blood cell volume, and helps regulate haemoglobin levels (2). After birth, the umbilical cord stump dries and falls off in 5-15 days. World Health Organization (WHO) states that care of dry cord for neonates is essential, due to rise in infections related to umbilical cord (3).

Omphalitis is a rare but severe postpartum localised infection of the umbilical cord stump and periumbilical soft tissue that occurs during the gestation period (4). If treated late, neonatal mortality rates from this illness could vary from 7% to 15% (5). According to a case report, periumbilical necrotizing fasciitis (NF) can result from neonatal omphalitis. The soft tissues of muscle fascia are primarily infected by bacteria. Compared to developing nations, developed nations have considerably better prediction statistics for NF bacterial infections. Despite therapy and prediction, the mortality rate is relatively high. Consequently, it is a rare infection that draws late attention from physicians (6).

2. Normal vs infected umbilical cord

The length of normal umbilical cord is approximately 55 cm in size. It gradually dries up and falls off in 3 weeks. Small mark of belly button is left behind. Infected neonatal umbilical cord is caused due to bacterial infection. Two factors create highly favourable milieu in necrotic tissues for bacteria to grow: (i) a typical spontaneous vaginal delivery; and (ii) the environment and treatment after delivery (4).

3. Etiology

Bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* are the root causes of omphalitis (7,8). *Bacteroides fragilis*, *Clostridium perfringens*, *Clostridium tetani*, and other facultative, anaerobic bacteria may sometimes be the cause of infection. Omphalitis and NF infections can potentially be caused by indirect maternal infection (chorioamnionitis)(9).Other factors include premature leakage of amniotic fluid, umbilical catheterization as well as home birth delivery still prevalent in underdeveloped countries. Cases of omphalitis may progress to umbilical melanoma owing to delayed or false diagnosis (10).

4. Signs-symptoms and diagnosis

Discoloration of skin or red patches surfaces as primary symptoms to infections usually observed for visual diagnosis of omphalitis. Thick peri-umbilical skin with fluid-leaky umbilical stump with foul odour is one of the distinguishing symptoms. Usually, it is observed that infants cry when the umbilical stump or skin around it is touched (9). Other symptoms like lethargy and high fever are also observed (10). Infection may be transfered from mother to child before birth or during delivery. This is due to various bacteria situated in vagina during gestational period, premature birth, infection in placenta, etc. Also, bacterial infection might spread around umbilical cord stump due to use of medical equipment like catheters, after birth. Detailed evaluation and confirmatory tests of neonatal sepsis are performed using tests as depicted in Figure 1.

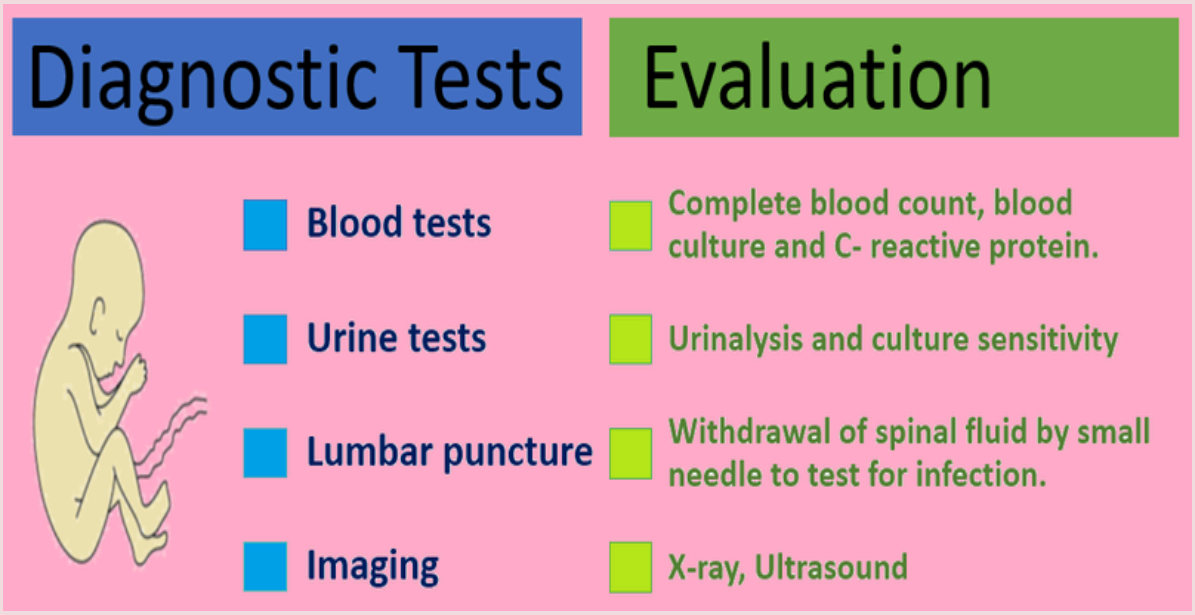

Figure 1. Diagnostic evaluation tests for Omphalitis and NF infections

5. Treatment

If umbilical infection is observed in infants, hospitalization in a tertiary health institution is necessary for treatment (4). Antibiotics like ampicillin, cloxacillin, gentamicin, amikacin, cefotaxime, vancomycin and imipenem are mostly prescribed; yet, employing their judicious therapeutic regimen is challenging. Also, these may cause high antibiotic resistance to isolated organisms. The primary cause of omphalitis is usually Staphylococcus aureus, which is fairly responsive to drugs like imipenem and cefotaxime. For omphalitis, combination antibiotic therapy is therefore highly recommended in order to minimise antimicrobial resistance (11). For sepsis treatment, antiseptic agents are used as it has bactericidal and bacteriostatic properties. Chlorhexidine known for its antiseptic property is recommended in safe concentrations. It strongly binds to negatively charged cell wall of microorganisms and alters the osmotic balance of the causative pathogen (12). Broad-spectrum applications for methylated spirit include bactericidal, mycobacterial, fungicidal, and viricidal effects. It causes lipid coagulation, denatures the protein, impairs cellular metabolism, and ultimately kills microorganisms (13).Thus, both chlorhexidine and methylated spirit can be used in the treatment of omphalitis and NF. Researchers and healthcare experts recommend parental education, awareness following treatment and discharge to lower the rate of morbidities, and ultimately decrease mortality (14). Few questions about the hand washing habits of birth assistants, clean delivery kits, skincare routines, mother-infant contacts, and use of various other applications like mustard oil, ash, mud, antiseptics as they are used in home-based deliveries were observed when data on risk factors for omphalitis was collected from Nepal (15).

6. Clinical trials in different countries

An estimated 3.7 million new-born deaths annually are attributed to various infections (3). Tokyo medical professionals described a case involving a 6-day-old female new born. Her umbilical cord was seen to be dry, black in colour, with redness and swelling surrounding it without pus. After a number of laboratory tests, omphalitis was identified. Thus, intravenous cefotaxime and vancomycin treatment were initiated. A variety of cultures of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and Entero bacteriaceae were used to examine the peri-umbilical swab and blood sample. Swelling around the abdomen appeared to be expanding. Consequently, meropenem was used instead of antibiotics in treatment. With hypotensive shock and hypothermia, the condition of the new-born worsened. NF was confirmed by computed tomography (CT). The area of perfusion was assessed intravenously using indocyanine green. Necrotic skin was surgically treated. Physicians handled the case of omphalitis with surgery followed by apt treatment of antibiotics. The case report highlights the need for physicians as well as pharmacists to be knowledgeable about the risk factors and possibility of getting NF (6). Different countries have already conducted clinical trials for omphalitis as exhibited in the tabulated data represented in Table 1.

Table 1. Data on clinical trials for omphalitis cases

Country	Clinical study type	Etiology	Outcomes	Ref
Nepal	Cluster-randomized study (Community based trial)		• Cord care is divided into two types i.e. use of 4% chlorhexidine cleaning and other by soap-water or dry cord care. • These cares reflected the umbilical cord separation time in infants. • As per clinical study, cord separation duration was less for dry cord care / soap-water (4.25 days) compared to chlorhexidine (5.32 days).	(16)

Western Uganda	Cross-sectional study (Hospital-based trial)	*Staphylococcal aureus, Neisseria species E. coli Proteus species, Klebsiella species, Citrobacter species, Haemophilus species*	• Study was conducted in a hospital of western Uganda in which neonates with omphalitis infection were selected and clinical diagnosis was carried out. • Umbilical cord swab was assessed for etiology. • *Staphylococcal aureus* was primary reason to omphalitis infection. • Isolated species were resistant to ampicillin, gentamicin and cloxacillin antibiotics.	(11)
Eastern Turkey	Survey in department of paediatrics	*Staphylococcus aureus, Escherichia coli*	• The survey stated that nearly 7.7% cases occurred every year in hospital born neonates. Highest morbidity rate was reported to be 15%. • Infection increases with septic delivery (home delivery). • Clinical reports of WBC and neutrophil count in blood were in normal limits. • Pathological test reveal that *Staphylococcus aureus* was the most common microorganism detected. • Also, physicians concluded that aseptic delivery technique should be adapted with all the basic care of umbilical cord. • Antibiotic therapy was advised if infection was confirmed, in addition to umbilical stump care using alcohol, chlorhexidine, and hexachlorophene	(17)
North-Central Nigeria	A Randomized study (Non-inferiority Trial)		• A comparative analysis of 96% methylated spirit and an antiseptic agent with 4% chlorhexidine was done during 28 days trial. • 96% methylated spirit showed more effect than chlorhexidine. • It reported that 4% chlorhexidine showed the peri-umbilical cord acne (lesions with pus). • Thus, methylated spirit is more effective, safe, tolerable and cost effective than chlorhexidine in preventing omphalitis infection.	(13)
Pakistan	Community-based (cohort study)	*Staphylococcus aureus, Pseudomonas species, Aeromonas species, Klebsiella species*	• Infection cause due to *Staphylococcus aureus* species. • Preventive measures are required with proper diagnosis, proper medication. • This will eventually decrease the rate of neonatal mortality due to NF and omphalitis. • Use of chlorhexidine gels can help to avoid infections.	(18)

7. Future omphalitis therapy: Advancing stem cell therapies

Self-renewal and the capacity to develop into a particular adult cell type are the two distinct features that define stem cells. Pluripotent and multipotent stem cells are the two different types of stem cells. Pluripotent stem cells can develop into any type of adult cell; exists for a short period of time. Additionally, the cells differentiate further into strong tissues and cell lines. Pluripotent cells can therefore, develop into any type of multipotent stem cell. Researchers discovered that various diseases are treated by multipotent stem cells (19). Hematopoietic stem cells are multipotent stem cells found in umbilical cord blood. These can be transplanted for treatment of malignant and non-malignant disorders along with hematologic, immunologic and inherited metabolic disorders. As umbilical cord blood, high in CD34+ is widely used in immunotherapy (20). Therefore, transplanting hematopoietic stem cells is thought to be a form of therapy for treating omphalitis and NF.

The placenta and umbilical cord are discarded when neonates are born. However, blood remaining in the umbilical cord is extracted, examined and kept in a cord bank for future use in order to preserve stem cells. Many public and private umbilical cord blood banks are situated worldwide to get benefit of it. Cryopreservation is a technique in which the umbilical blood is stored in liquid nitrogen (−196°C) (21,22). Generally private and public cord banks are associated with storage of cord blood. Public cord banks of India are as follow:

- The Reliance Dhirubhai Ambani Life Sciences Center in Thane, Maharashtra
- Jeevan Stem Cell Bank, Tamil Nadu
- The School of Tropical Medicine (STM), Kolkata
- StemCyte Inc., Apollo Hospital Enterprises Ltd.

Thus, umbilical cord blood-derived hematopoietic stem cells exhibit considerable potential in omphalitis and NF treatment.

8. Conclusion

Omphalitis is a rare neonatal infection, often caused by *Staphylococcus aureus*, which can lead to severe complications such as necrotizing fasciitis. Understanding its etiology, diverse clinical presentations, and diagnostic approaches is crucial for effective management and timely treatment. Clinical cases from different regions highlight the global impact of omphalitis and the variability in treatment strategies. Furthermore, exploring the potential use of umbilical cord blood stem cells as a future therapeutic option offers promising prospects for personalized medicine in addressing omphalitis-related complications. Continued research and clinical efforts are necessary to improve outcomes and reduce the burden of this orphan disease.

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Cystic fibrosis: A rare disease


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Abstract
Cystic fibrosis (CF) is a hereditary autosomal recessive disease predominantly affecting Caucasian children and young adults. It arises from mutations in the CFTR (Cystic fibrosis transmembrane Conductance regulator) gene, leading to thick, sticky mucus accumulation and subsequent organ damage, primarily in the lungs and digestive system. Diagnostic methods include neonatal screening, sweat chloride tests, and genetic testing. Management focuses on clearing airways, preventing infections, and maintaining nutrition. Emerging treatments target CFTR gene mutations, including gene therapy and genome editing. This review summarizes CF's background, prevalence, etiology, complications, diagnosis, treatments, and future research directions.

Keywords: Cystic fibrosis, CFTR gene, Pulmonary complications, Genetic testing, Therapeutic interventions

1. Introduction
Cystic fibrosis (CF) is a complex and chronic genetic disorder characterized by a malfunction in the CFTR gene, located on chromosome 7, which encodes the CF transmembrane conductance regulator protein. This protein plays a crucial role in regulating ion transport across epithelial cell membranes in various organs. In CF, the dysfunction of CFTR leads to altered ion transport, particularly affecting the respiratory and digestive systems, as well as the sweat glands and reproductive system in most cases. The disease typically manifests early in life, during infancy, and presents with a wide range of symptoms. The classic phenotype includes progressive obstructive pulmonary disease, exocrine pancreatic insufficiency, and elevated sweat chloride and sodium levels, observed in the majority of patients. Despite advances in treatment and management, CF remains a chronic and progressive illness, often with a reduced lifespan. On average, individuals with CF have a lifespan of approximately 30 years. While CF-like symptoms have been recognized for over two centuries, the term "cystic fibrosis" was formally coined in 1938 to describe the disease's characteristic pancreatic involvement. Today, ongoing research continues to improve our understanding of CF and develop new therapies to enhance the quality of life and longevity for those affected by this condition (1-6).

2. Epidemiology
Cystic fibrosis (CF) presents a complex picture of prevalence, affecting primarily Caucasians but also occurring in other racial and ethnic groups, albeit less frequently. In the United States, approximately 30,000 Americans, along with 3,000 Canadians and 20,000 Europeans, grapple with CF, while an alarming 12 million individuals in the U.S. unknowingly carry an abnormal CF

gene.Globally, prevalence rates vary, from 1 in 1,400 in Ireland to 1 in 3,500 in the U.S., with lower rates observed in regions like Asia and Africa (7). In Latin America, CF affects 1 in 1,600 to 14,000 live new-borns, with a detection rate of pathogenic variants around 41.6% (8). Mortality in childhood primarily stems from respiratory infections and malnutrition due to pancreatic insufficiency, particularly in resource-limited countries like Mexico and Latin America, though advancements in therapies have extended survival to an average of 18 years. In developed nations such as Canada, the U.S., and the U.K., where advanced treatments are accessible, life expectancy exceeds 40 years, with long survivors living beyond 47 years, underscoring the impact of improved therapies on enhancing CF patient lifespan (9,10).

3. Genetic inheritance

Cystic fibrosis (CF) is a monogenic autosomal recessive genetic disorder, indicating that offspring resulting from a union between a mother who is a carrier of the CF gene and a non-carrier father have a 50% probability of inheriting the carrier status and a 50% probability of remaining unaffected. Similarly, in cases where both parents carry the CF gene, their offspring have a 25% likelihood of being unaffected, a 50% likelihood of inheriting the carrier status akin to their parents, and a 25% likelihood of manifesting CF symptoms. This genetic inheritance pattern underscores the necessity for comprehensive genetic counselling and testing to ascertain CF risk within familial contexts (11).

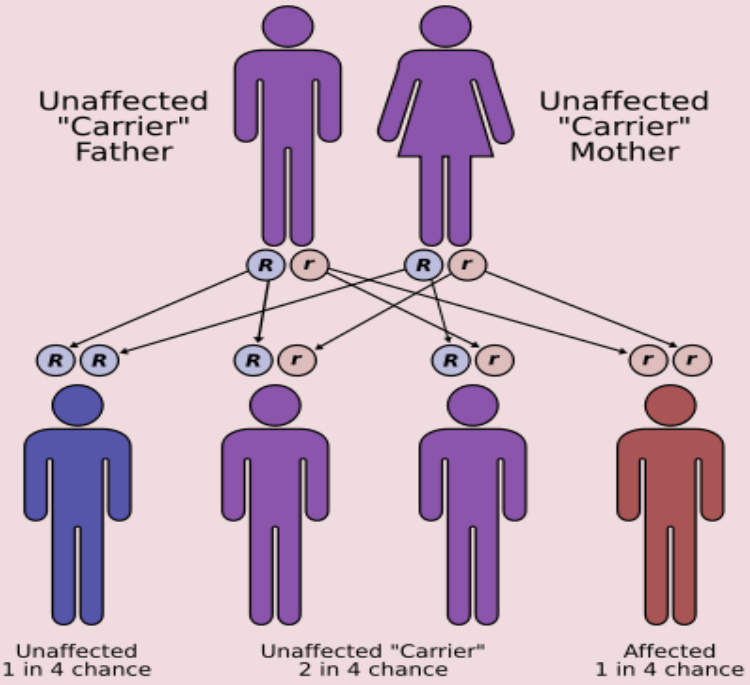

Figure 1. Autosomal recessive cystic fibrosis (12)

(Source: Disabled World. (2022, April 13)

4. Symptoms

- Salty-tasting skin on kissing
- Persistent coughing, at times with phlegm
- Frequent lung infections including pneumonia or bronchitis
- Wheezing or shortness of breath
- Poor growth or weight gain in spite of a good appetite (13,14)

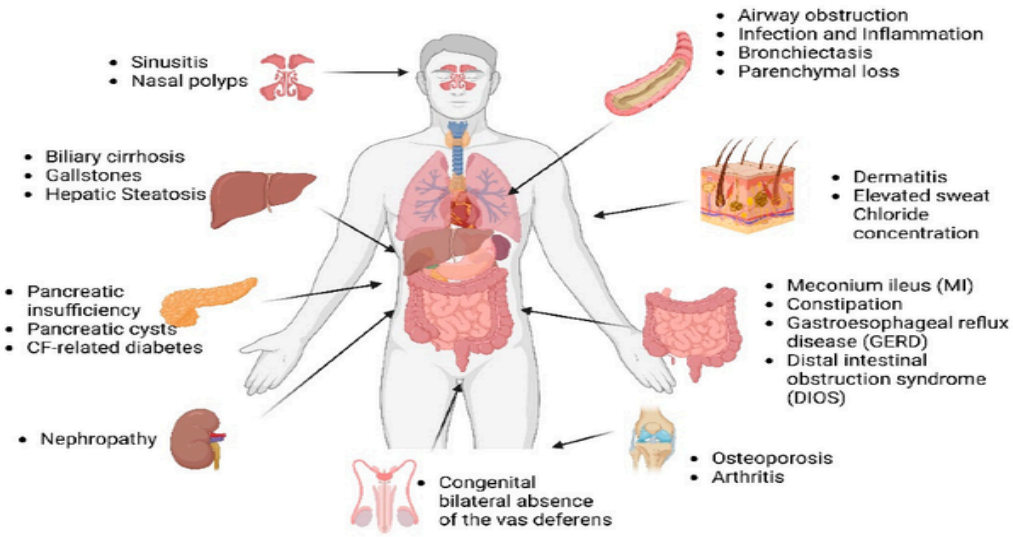

Figure 2. Symptoms of cystic fibrosis (15)

(Source: Ramananda Y, Naren AP, Arora K. Functional Consequences of CFTR Interactions in Cystic Fibrosis. Int. J. Mol. Sci. 2024;25:3384)

5. Diagnostic methods

Diagnosing cystic fibrosis (CF) involves several tests to identify its characteristic features.

5.1 **Sweat electrolyte level measurement**: Elevated chloride levels (>60 mmol/L) indicate CF.
5.2 **Salty skin test**: Infants with CF may exhibit salty skin when kissed, serving as a notable sign of the disease.
5.3 **Newborn screening**: Utilizes the Guthrie blood spot test followed by genetic testing for CFTR gene mutations, commonly conducted in the UK.
5.4 **Blood tests**: Assess immunoreactive trypsinogen levels, aiding in CF diagnosis.
5.5 **Chest X-rays**: Show lung inflammation, fibrosis, and scarring indicative of CF-related airway obstruction and lung infections.
5.6 **Sinus X-rays**: Reveal signs of sinusitis, another common manifestation of CF.
5.7 **Lung function tests:** Evaluate respiratory function, assisting in CF diagnosis and monitoring.
5.8 **Sputum cultures:** Identify pathogens responsible for lung infections in CF patients.
5.9 **Genetic testing:** Crucial for detecting CFTR gene mutations, with PCR and DNA sequencing being common methods.
5.10 **Comprehensive tests:** Such as the Ambry Test, employing temporal temperature gradient electrophoresis analysis and DNA sequencing, may be necessary due to the extensive mutation spectrum of the CFTR gene.
5.11 **Combined approach**: Utilizing clinical, radiographic, and genetic tests is vital for accurate CF diagnosis and management. (16-18)

6. Management and treatment

Cystic fibrosis (CF) management primarily focuses on symptom control, complication prevention, and improving patients' quality of life, as there is presently no cure for the condition. To combat lung infections, a variety of antibiotics are prescribed depending on the severity, with options including azithromycin, tobramycin, aztreonam, levofloxacin, ciprofloxacin, cephalexin, amoxicillin, and doxycycline. These antibiotics are administered orally or through inhaled forms to target respiratory inflammation and prevent infections (19,20). Bronchodilators, such as beta-agonists, are also utilized to dilate airways and reduce the viscosity of mucus in the lungs, aiding in its clearance. Inhaled Dornase Alfa, or pulmozyme, is another treatment option that breaks down excess DNA in pulmonary secretions, lowering the risk of respiratory tract infections (21,22).

For gastrointestinal issues commonly associated with CF, treatment includes oral rehydration therapy to combat dehydration, osmotic laxatives to soften stools, and hyperosmolar contrast enemas for distal intestinal obstruction syndrome (DIOS). Pancreatic enzyme replacement therapy (PERT) is crucial for overcoming pancreatic insufficiency, allowing for better absorption of nutrients. PERT supplements contain enzymes to aid in the digestion of proteins, carbohydrates, and fats, preventing malabsorption and malnutrition. Additionally, CF patients require a specialized diet rich in calories, vitamins (A, D, E, K), minerals, and sodium chloride supplementation, tailored to their individual needs and environmental conditions.

Supportive therapies play a significant role in managing CF symptoms and improving overall well-being. These include airway clearance techniques using bronchodilators, mucolytic agents, and various devices, as well as the use of steroid inhalers to reduce inflammation. Recombinant human DNase I (rhDNase I) inhalation is also utilized to assist in mucus clearance. Moreover, recent breakthroughs in CF research have led to the development of CFTR modulators, drugs that target the specific gene defect underlying CF. While the long-term benefits of these medications are still being studied, and initial clinical trials have shown promise in slowing disease progression in the lungs, potentially enhancing the quality of life for CF patients (23-25).

7. Conclusion

Cystic fibrosis (CF) is a complex genetic disorder caused by mutations in the CFTR gene, leading to defective ion transport across epithelial cell membranes and affecting the respiratory and digestive systems. Diagnosis involves sweat tests, genetic screening, and various imaging and lab tests to confirm CFTR mutations and characteristic symptoms. Although there is no cure for CF, treatment advances have greatly improved life expectancy and quality of life. Management focuses on symptom control and complication prevention through antibiotics, bronchodilators, mucolytics, enzyme replacement therapies, and specialized diets. Supportive therapies, including airway clearance techniques and CFTR modulators, further enhance patient outcomes. These therapeutic advancements have increased survival rates and improved the quality of life for CF patients, especially in developed countries. Ongoing research continues to offer hope for further improvements in managing and treating cystic fibrosis.

8. Future considerations

Advancements in cystic fibrosis (CF) treatment focus on addressing the disease's root causes rather than solely managing symptoms. By targeting early abnormalities in CF's pathophysiology, there's hope to improve outcomes and reduce treatment burdens. Therapeutic approaches like messenger RNA therapy, DNA/gene therapy, and gene editing aim to correct structural and functional CFTR protein abnormalities. While CFTR modulators offer relief, limitations such as variable efficacy and cost considerations persist. Screening initiatives for parents and prenatal molecular screening may help reduce CF's population burden. The ultimate goal is to develop interventions effectively halting or slowing disease progression, offering hope for enhanced quality of life for CF patients.

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An overview on cystic fibrosis: Comprehensive insight and current developments

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1. Introduction

Cystic fibrosis (CF) is a genetic disorder that significantly impacts the respiratory and digestive systems affecting approximately 70,000 people globally. It's well known that orphan diseases are conditions that affect a small percentage of the population, often lacking sufficient treatment options. Likely, CF is also classified as an orphan disease in many countries due to its rarity (1-3). This article aims to provide a comprehensive understanding of cystic fibrosis, its impact as a rare disease, its genetic basis, symptoms, diagnosis, treatment options, and the latest research developments.

2. Understanding cystic fibrosis

Cystic fibrosis is an inherited disorder resulting from mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene. This gene is responsible for encoding a protein that controls the flow of salt and water into and out of cells. When this gene is mutated, it leads to the production of thick and sticky mucus, which can cause severe damage to the respiratory and digestive systems (1-4).

3. Genetic basis and inheritance

Genetic mechanism

CF is an autosomal recessive disorder, meaning a child must inherit two defective copies of the CFTR gene, one from each parent, to develop the disease. Individuals with only one defective gene are carriers and typically do not show symptoms but can pass the gene to their children (4,5).

Table 1. Genetic Inheritance of Cystic Fibrosis *(Source: Cystic Fibrosis Foundation)*

Parents' Genetic Status	Probability of Child with CF	Probability of Carrier Child	Probability of Non-Carrier Child
Both parents carriers	25%	50%	25%
One parent carrier	0%	50%	50%
Neither parent carrier	0%	0%	100%

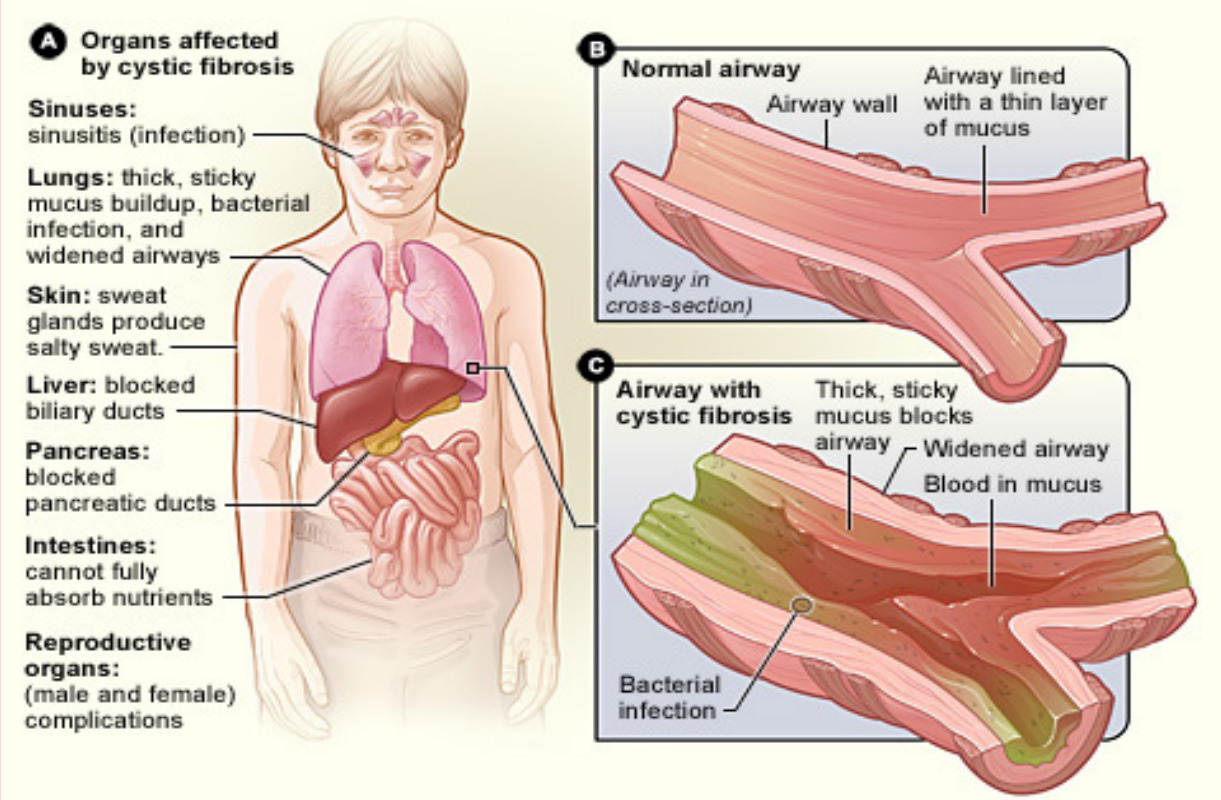

Figure 1. How CF Affects the Body (Source: Cystic Fibrosis Foundation)

4. Symptoms and diagnosis

4.1 Symptoms

The symptoms of cystic fibrosis can vary widely among individuals, but they generally include:

- **Respiratory issues:** Chronic coughing, wheezing, and frequent lung infections such as pneumonia or bronchitis.
- **Digestive problems:** Poor growth, weight gain despite a good appetite, frequent greasy and bulky stools, and intestinal blockages.
- **Salty-tasting skin:** High salt levels in sweat.
- **Infertility in males:** Due to blockage or absence of the vas deferens.

4.2. Diagnostic Methods

CF is typically diagnosed through a combination of tests:

- **Newborn Screening**: Conducted at birth to identify CF early.
- **Sweat Test**: Measures the concentration of salt in sweat, which is elevated in CF.
- **Genetic Testing**: Identifies mutations in the CFTR gene.

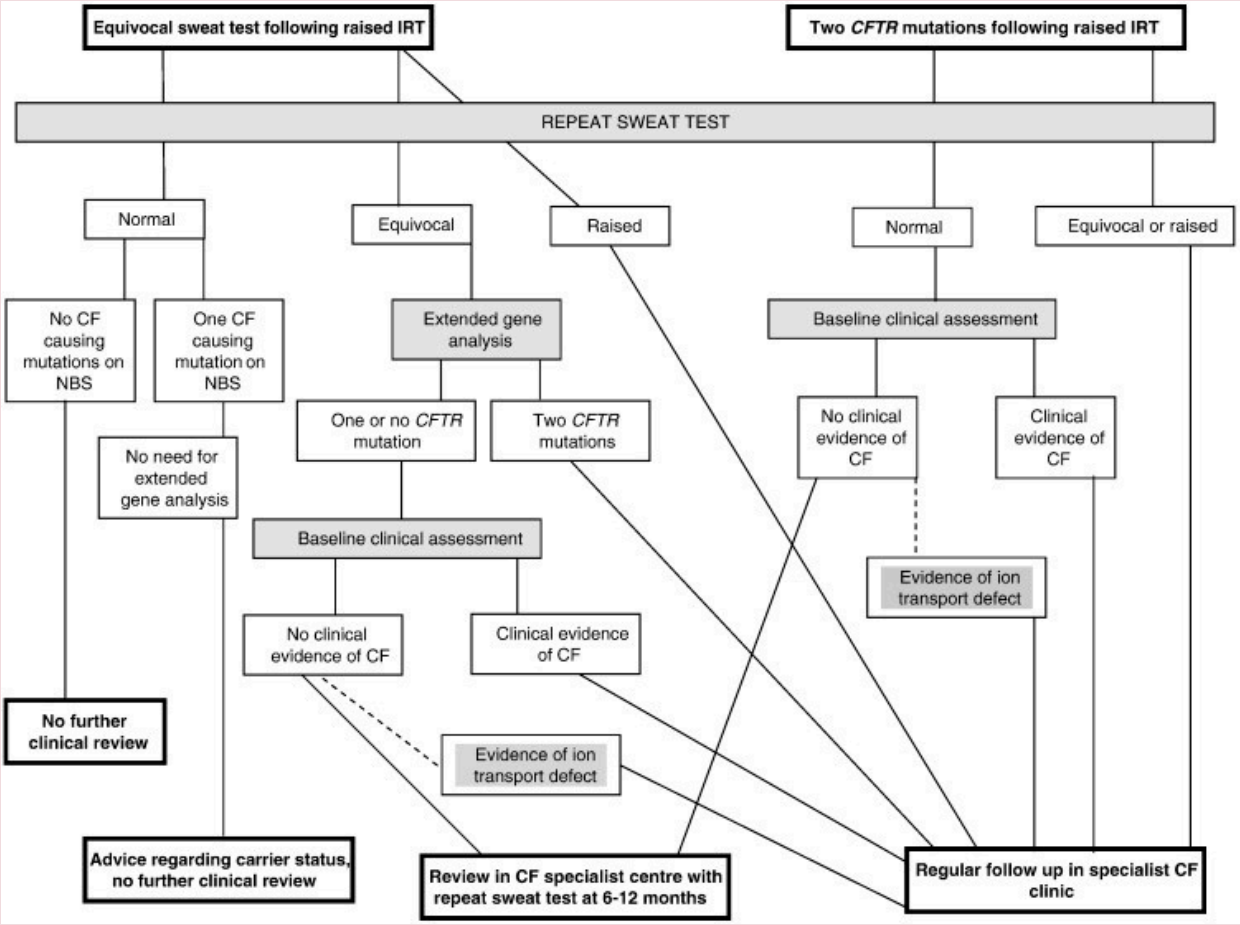

Figure 2. Diagnostic Pathway for Cystic Fibrosis (Source: Cystic Fibrosis Foundation)

5. Medication for cystic fibrosis

Treatment for CF typically involves a combination of therapies aimed at managing symptoms, preventing complications, and addressing the underlying genetic cause. The following categories of medications are commonly used (6-14).

5.1 CFTR modulators

CFTR modulators are a recent advancement in CF treatment. These drugs target the defective CFTR protein, improving its function. Types of CFTR modulators include:

- **Ivacaftor (Kalydeco):** Works by improving the function of the CFTR protein at the cell surface. It is effective for people with specific CFTR mutations (e.g., G551D).
- **Lumacaftor/Ivacaftor (Orkambi):** Combination therapy for individuals with two copies of the F508del mutation. Lumacaftor helps the CFTR protein reach the cell surface, and Ivacaftor enhances its function.
- **Tezacaftor/Ivacaftor (Symdeko):** Similar to Orkambi, it helps the CFTR protein to reach the cell surface and function properly, suitable for certain mutations including F508del.
- **Elexacaftor/Tezacaftor/Ivacaftor (Trikafta):** A triple combination therapy for individuals with at least one F508del mutation, it significantly improves lung function and quality of life.

5.2 Antibiotics

Used to treat and prevent lung infections. They can be administered orally, inhaled, or intravenously depending on the severity of the infection.

- **Tobramycin** (inhaled): Commonly used to treat chronic *Pseudomonas aeruginosa* infections.
- **Azithromycin:** An oral antibiotic that also has anti-inflammatory properties.

5.3 Mucus thinners

These medications help to thin and loosen the thick mucus in the lungs, making it easier to clear.

- **Dornasealfa (Pulmozyme):** An inhaled medication that breaks down DNA in the mucus, reducing its viscosity.
- **Hypertonic saline:** An Inhaled saline solution that helps draw water into the airways to thin the mucus.

5.4 Anti-inflammatory medications

Reduce inflammation in the lungs to prevent damage.

- **Ibuprofen:** High-dose ibuprofen can slow the decline of lung function in some children with CF.
- **Corticosteroids:** Used less frequently due to side effects, but can be beneficial in certain situations

.

5.5 Bronchodilators

Help open the airways by relaxing the muscles around them, making it easier to breathe.

- **Albuterol:** Often used before airway clearance therapies to open the airways.

5.6. Digestive enzymes

Since CF can block the pancreas, leading to malabsorption, pancreatic enzyme replacement therapy is crucial.

- **Pancrelipase (Creon, Pancreaze):** Helps digest food and absorb nutrients.

5.7. Vitamins and supplements

People with CF often require fat-soluble vitamins (A, D, E, and K) due to malabsorption.

5.8 Other therapies

- **Airway clearance techniques (ACTs)**: Chest physiotherapy and mechanical devices that help to clear mucus from the lungs.
- **Nutritional support**: High-calorie nutritional plans and vitamins.
- **Lung transplantation:** In extreme conditions, individuals with cystic fibrosis may undergo lung transplantation as a treatment option.

6. Management of cystic fibrosis

Management of CF is comprehensive and typically involves a multidisciplinary approach. Regular monitoring and proactive treatment adjustments are essential to address the changing needs of individuals with CF. Research is ongoing to find better treatments and ultimately a cure for this condition.

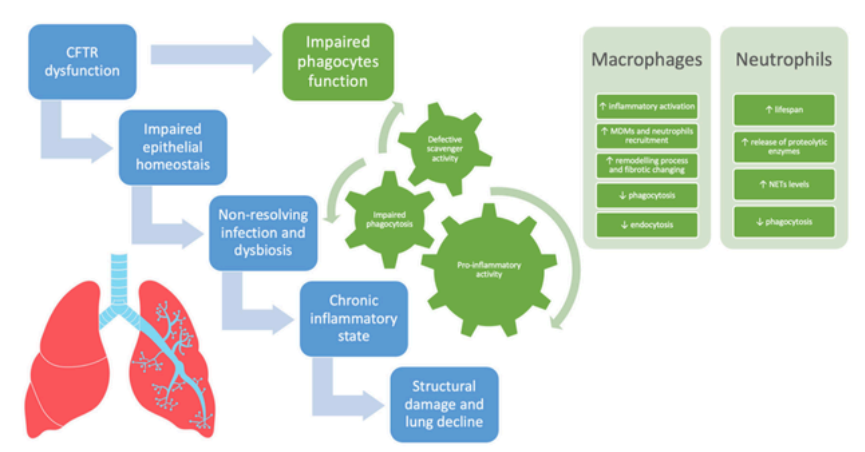

Figure 3. Impact of CFTR Modulators (Source: Cystic Fibrosis Foundation)

Table 2. Common CF Treatments (Source: Cystic Fibrosis Foundation)

Treatment Type	Description	Purpose
Airway Clearance Techniques	Methods to loosen and remove mucus	Improve breathing and reduce infection
Inhaled Medications	Bronchodilators, antibiotics, hypertonic saline	Open airways, fight infection, thin mucus
Pancreatic Enzymes	Supplements to aid digestion	Improve nutrient absorption
CFTR Modulators	Drugs targeting the defective CFTR protein	Improve lung function and overall health

7. Living with cystic fibrosis

7.1 Daily management

Managing CF involves a rigorous daily regimen, including airway clearance, medication adherence, and regular check-ups. Nutritional support is essential due to challenges with nutrient absorption, necessitating a high-calorie, high-fat diet (2).

7.2 Psychological and social support

The chronic nature of CF can affect mental health. Access to psychological support, counselling, and CF-specific support groups is vital. These resources help patients and their families cope with the emotional and social challenges posed by the disease.

8. Prognosis

The prognosis for individuals with CF has improved significantly over the past few decades due to advances in treatment. The average life expectancy has increased, with many individuals living into their 30s, 40s, and beyond. Continuous medical advancements and comprehensive care are key factors in enhancing both lifespan and quality of life for those with cystic fibrosis (2,3).

9. Research and future directions

9.1 Ongoing research

Research is focused on finding better treatments and a potential cure for CF. Key areas include:

- **Gene Therapy**: Strategies to correct the defective CFTR gene.
- **Stem Cell Therapy**: Potential to regenerate damaged tissues.
  Advanced CFTR Modulators: Developing drugs that target a broader range of CFTR mutations.

9.2. Promising developments

Recent advances in gene editing technologies, such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), show promise for directly correcting CFTR mutations. Ongoing clinical trials are exploring these innovative treatments' safety and efficacy.

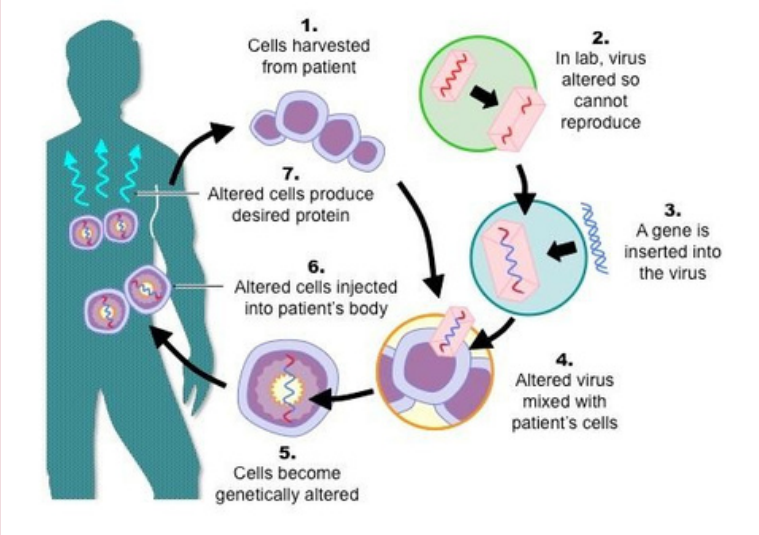

Figure 4. Gene Therapy Process (Source: National Human Genome Research Institute)

Conclusion

Cystic fibrosis is a challenging condition, but advancements in treatment and research provide hope for better management and, eventually, a cure. Continued support and awareness are essential to improving the lives of those affected by CF. For the latest information on CF and its treatments; it's always advisable to consult resources like the Cystic Fibrosis Foundation or a healthcare provider specializing in CF care.

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Exploring rare genetic disorders: Insights into Moebius syndrome and Progeria syndrome


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Abstract
Rare diseases present significant challenges in healthcare due to their diverse symptoms, limited scientific understanding, and inadequate treatment options. Moebius Syndrome and Hutchinson-Gilford Progeria Syndrome (HGPS) are two such rare conditions that illustrate the complexities and impact of these disorders. Moebius Syndrome, characterized by facial and ocular nerve paralysis, poses challenges in diagnosis and management due to its genetic and environmental origins. Similarly, HGPS, a genetic disorder causing premature aging symptoms, underscores the urgent need for effective treatments. Despite their rarity, these diseases profoundly impact patients' quality of life, emphasizing the importance of heightened awareness, research collaboration and equitable access to healthcare. Additionally, involving affected individuals in clinical trials can improve research investigations and

Keywords: Rare disease, Moebius, Progeria, Genetic, Healthcare

1. Introduction

Over 7,000 known rare diseases affect approximately 400 million people worldwide. These conditions collectively represent one of the largest underserved patient communities globally. It's noteworthy that 80% of rare diseases are of genetic origin, with half of them affecting children, which emphasizes the profound impact on individuals and families. Despite their prevalence, medical expertise, knowledge, and care offerings for rare diseases remain scarce, resulting in delays in diagnosis, inadequate treatment options, and limited research efforts (1,2).

2. Moebius syndrome

Moebius syndrome is rare congenital disorder characterized by unilateral or bilateral non-progressive facial nerve paresis (Nerves VII) and impaired ocular abduction due to dysfunction of the abducens nerve (Nerves VI). German neurologist Paul Julius Moebius provided the first detailed clinical description in 1888, noting facial and abducens nerve paralysis, while Von Graefe initially reported facial muscle weakness. In addition, Moebius syndrome can also affect other cranial nerves, leading to orofacial, behavioral, cognitive, and orthopedic issues like conjoined fingers/ toes or brachydactyly (4-6). Manifestations encompass facial muscle weakness, speech challenges, dental issues, and hand anomalies (7-10). Figure 1 shows the facial changes before and after due to Mobius syndrome.

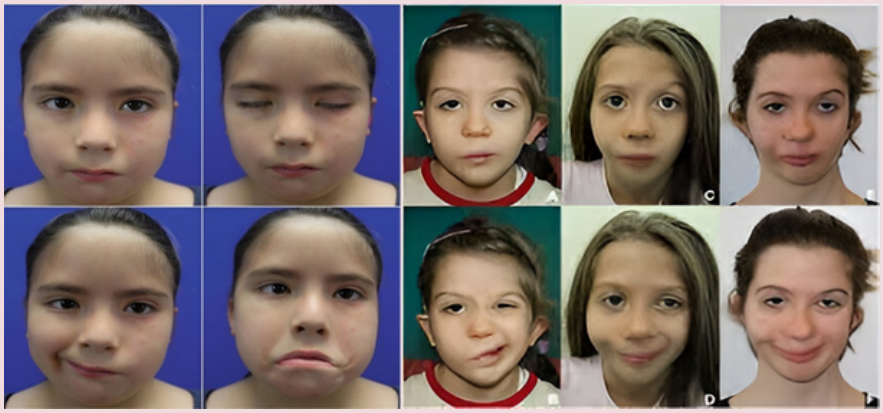

Figure 1. Facial changes due to Mobius syndrome in individuals (Source: https://samarpanphysioclinic.com/moebius-syndrome)

2.1 Role of genetics

Genetics plays a significant role in the etiology with reported genetic loci at 3q21-q22 and 10q. Mutations in genes such as REV3L, PLXND1, HOXA1, HOXB1, and TUBB3 have been associated with facial palsy in Moebius syndrome (11). While familial patterns exist in rare cases, they are mostly sporadic, suggesting a complex genetic basis. Additionally, factors like intrauterine infections, hyperthermia, trauma, and exposure to teratogens may also contribute to the development of disease (12).

2.2 Management/treatment

The management of Moebius syndrome requires a multidisciplinary approach involving healthcare professionals, neurologists, orthopedic surgeons, ophthalmologists, and speech therapists. Specialized feeding techniques and nutritional support may be necessary for infants experiencing sucking and feeding issues. Surgical interventions, such as facial reanimation surgery, can improve facial movements and symmetry, while ophthalmological assessment can prevent corneal ulceration and correct ocular abnormalities like strabismus and lagophthalmos (13, 14).

3. Hutchinson-Gilford progeria syndrome

Hutchinson-Gilford Progeria Syndrome is a genetic disorder characterized by symptoms of accelerated aging, affecting approximately 1 in 4-8 million children. It is caused by a mutation in the LMNA gene, leading to the production of a truncated protein called progerin, whose accumulation causes defects in nuclear envelope structure and function, resulting in premature aging, impaired DNA repair, increased ROS production, and mitochondrial dysfunction in HGPS cells. HGPS is not typically inherited; the genetic change usually occurs randomly, making it extremely rare. If a family has previously had a child with HGPS, the chance of having another affected child increases to about 2-3% due to mosaicism (15, 16). Figure 2 show the characteristics of the disease.

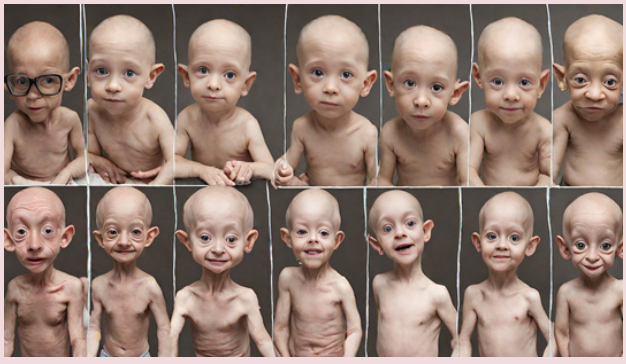

Figure 2. Disease the progression of Progeria from childhood till later age (Figure source: AI generated)

3.1 Role of genetics

Genetics plays a crucial role in Progeria syndrome, particularly in HGPS. The LMNA gene mutations, such as the de novo C1824T mutation, lead to the accumulation of progerin, a dominant negative form of lamin-A, causing premature aging. Genes like KRT8, KRT18, ACKR4, CCL2, UCP2, ADAMTS15, ACTN4P1, WNT16, and IGFBP2 play a role in both progeria syndrome and natural aging, indicating genetic involvement in progeria. This accumulation of progerin alters the organization of the nuclear lamina and chromatin, contributing to faster cellular senescence and the progeroid phenotype (17-19).

3.2 Management and treatment

Research on treating HGPS has mainly focused on genetic and pharmacological interventions 94.6% and 5.4% involve other approaches. Protein farnesyl transferase inhibitors (FTIs) have been extensively studied, comprising 22.5% of treatment. Lonafarnib, an FTI, has shown promise in improving bone structure, audiological status, and neurologic function in children with HGPS (20, 21). Nucleic acid therapy has emerged with over 40% of studies exploring this approach. Strategies include prenatal genetic manipulation, and antisense oligonucleotide therapy (22, 23). Table 1 show various treatment regimens of Progeria.

Table 1. Various treatment regimens for Progeria syndrome

Type	Treatment regimen
Pharmacological treatment	The administration of both pravastatin and zoledronate in combination (24)
	Therapy involving rapamycin (25)
	Leptomycin B therapy (26)
	Therapy involving baricitinib(27)
	Treatment combining levamisole and ARL67156 (28)
	Administration of resveratrol (29)
	Therapy with temsirolimus (30)
	Use of metformin (31)
Protein therapy	Administration of recombinant IGF-1 (32)
Microbiota therapy	Fecal microbiota transplantation (33)
Nucleic acid therapy	Targeting methyltransferase Suv39h1 depletion (34)
	The genetic approach decreases the expression and activity of isoprenylcysteine carboxyl methyltransferase (ICMT)
	Genetic inhibition of DNA damage activity at telomeres

4. Conclusion

In conclusion, rare diseases like Moebius Syndrome and Hutchinson-Gilford Progeria Syndrome highlight the need for increased awareness, research collaboration, and equitable access to healthcare.

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Elesclomol: A study on copper induced melanoma treatment

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Abstract

Elesclomol is a novel anti-cancer drug that triggers apoptosis in cancer cells. It has been designated as a fast-track drug and an orphan drug by the United States Food and Drug Administration (USFDA). Elesclomol was seen to induce oxidative stress but now it is famous for its anti-cancer properties. The anti-cancer activity based on the proliferation of cancer on the mitochondrial membrane. Elesclomol induces cuproptosis which is a process of cell death due to accumulation of copper in the mitochondrial membrane.

Keywords: Elesclomol, Metastatic melanoma, Cuproptosis

1. Introduction

Elesclomol is a drug formulated by Synta Pharmaceuticals, initially for the treatment of malignant melanoma, later a chemotherapeutic adjuvant. Cancer cells preferentially produce energy through glycosis even in the presence of oxygen, although further studies have shown its link to proliferation of cancer cells in the mitochondrial membrane. This can damage the integrity, structure and the membrane potential of mitochondria leading to apoptosis and altered energy production. The anti-cancer property of Elesclomol was earlier recognised for its ability to accumulate oxidative species to induce oxidative stress ranging from the cell bounds, the mitochondrial membrane and DNA contents. Meanwhile, the property relies on its ability to move copper ions to induce cuproptosis. Copper is a trace element in the body and the accumulation of cupric ions can lead to cytotoxic situations by reactions between copper ions and proteins (1-3).

2. Melanoma

Melanoma is a type of skin cancer that develops due to pigment producing cells called melanocytes. The mechanism of melanoma involves mutations in the DNA of melanocytes due to Ultraviolet radiation exposure. This can cause disruptions in cell DNA and lead to uncontrolled growth and become cancerous cells. Lesions and moles on the surface of skin indicate tumors. Melanoma is also based on genetic inheritance and lifestyle disorders. There are two types of melanoma cancers – Benign and Malignant (Metastatic). Most tumors tend to be benign in skin cancers such as moles whereas the malignant cancers spread to various body parts through the process of metastasis. About 1 in 10 individuals get affected by metastatic melanoma, making it an uncommon disease. Patients with metastatic melanoma survive for a median of 8.5 months. Treatment often includes close observation, subjecting to chemotherapeutic agents like dacarbazine that shows a response rate of 15% to 20% is widely used. Dacarbazine is commonly used to treat cancers such as melanoma, Hodgkin's lymphoma and soft tissue sarcomas. It works as an alkylating agent that adds an alkyl group to the DNA chains, thus disrupting the genetic structure and preventing cancer cells from multiplying. Furthermore, it induced cell apoptosis by targeting rapidly dividing cells. Dacarbazine is generally administered intravenously but oral form such as Temozolomide is also used and shows a response rate of 20%. Temozolomide is recognised for its ability to penetrate the Blood Brain Barrier (BBB) and effects on central nervous system. Either of the drugs are always administered in a combination. Additionally, combination drugs such as cisplatin, carmustine, paclitaxel and docetaxel are administered. This led to introduction of combination chemotherapy including tamoxifen. Although it initially showed high response states, it was concluded that the presence of tamoxifen showed no greater change in responses. This led to studies pertaining to immunotherapy and bio chemotherapy to cytotoxic cell death studies for treatment of metastatic melanoma in patients. Furthermore, cell apoptosis using platinum and copper mediated ions was a subject that soon rose to interest amongst scientists. The use of accumulation of trace elements in the body leading to toxicity and expulsion of cancerous cells (4).

3. Pharmacokinetics

Elesclomol is administered intravenously, leading to rapid and complete bioavailability into systemic circulation. Elesclomol binds with cupric ions and form a permeable complex which upon entering the mitochondrial matrix reduces into cuprous oxide in the presence of the protein mitochondrial ferrodoxin I. Cuprous oxide ions can generate reactive oxygen species (ROS) via Fenton reaction. In this reaction, Cuprous oxide ions react with hydrogen peroxide to give hydroxyl radicals which are highly reactive ROS. They play a complex role in cancer cells as they are essential at low levels but high levels can cause damage to cellular components. Cuprous ions are also essential in metalation of cytochrome in the mitochondria. This occurs by reaction of metal cuprous ion into cytochrome proteins is crucial for electron transport chain in cellular respiration. In addition to that, they are required for the maturation of cuproenzymes, which refer to enzymes containing copper as a cofactor. During maturation, the copper ions are incorporated into the active site and participate in catalytic processes. Ceruloplasmin, another cuproenzyme metabolised primarily for iron metabolism of the body. Elesclomol undergoes hepatic metabolism and glomerular filtration in process of excretion (5).

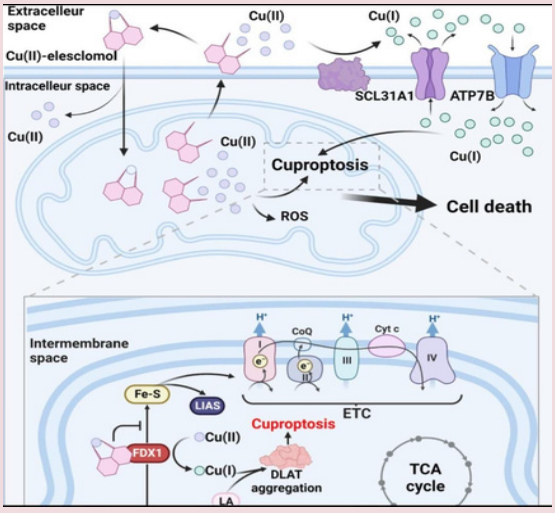

Figure 1. Cuproptosis mechanism

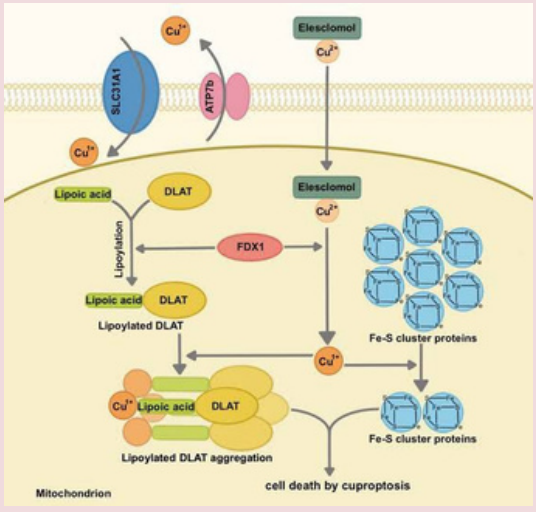

Figure 2. Copper pyrazole anti-cancer activity

4. Pharmacodynamics

Elesclomol biological effects revolve around inducing oxidative stress in cancer cells leading to mitochondrial dysfunction, affecting catalytic reactions, inhibiting angiogenesis, the process of formation of new blood vessels for metastasis, ultimately leading to apoptosis. Elesclomol in the bloodstream reacts with proteins such as Human Serum Albumin to serve as a carrier agent for distribution and availability in the body. Elesclomol interaction with the central nervous system, primarily the brain is very limited due to the poor blood brain barrier penetration of the drug. The drug interacts with the liver where it is subjected to hepatic metabolism and is converted to metabolites for excretion. Kidneys via glomerular filtration excrete the drug through urine. The dosages of Elesclomol varied as it is patient specific and ranges from 100 – 213 mg/m^2 in a treatment schedule every 3 weeks. The bioavailability of the drug administered through intravenous route is considered to be 100% as it directly enters bloodstream bypassing first pass metabolism (6).

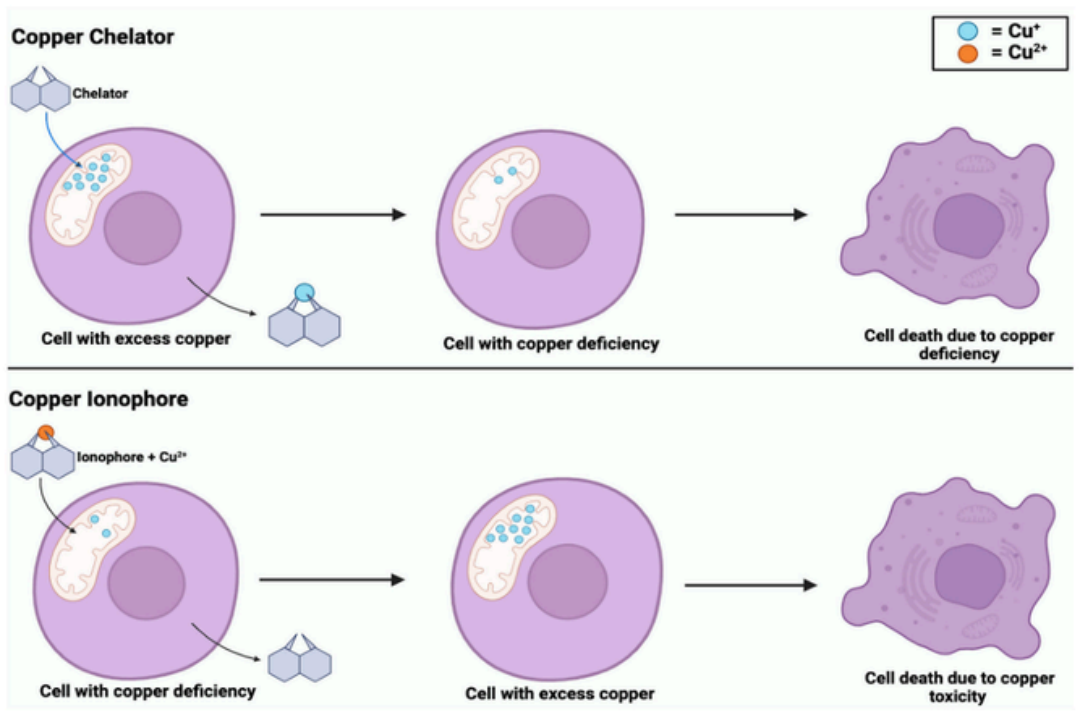

Figure 3. Cytotoxic death due to copper ions

5.Clinical trials and orphan designation

In preclinical models, the drug showed synergic bond with paclitaxel and docetaxel. In phase 1 study, the results obtained were partial response when patient was subjected to paclitaxel, intraperitoneal cisplatin, a sargramostim tumour vaccine, trabectedin, and liposomal doxorubicin. There were no recorded adverse side effects. 1,500 subjects had enrolled in clinical trials, and more than 600 subjects have received elesclomol as a single agent, or in combination with paclitaxel or docetaxel. More than 500 subjects were administered the elesclomol/paclitaxel combination at or above a dose of 213 mg/m2 given weekly for 3 weeks of a 4-week cycle. A phase 3 trial encompassing patients administered with 213 mg/m^2 of Elesclomol with 80 mg/m^2. The study was shortly terminated and abandoned as this dosage led to patient deaths and the risks of such and adverse reactions had no specific patterns. Shortly after, Elesclomol received orphan drug designation primarily as it was developed to treat rare cancer conditions like melanoma.

Orphan drug designation is granted by regulatory agencies like FDA for drugs intended for treatment, diagnosis and prevention of rare diseases that affect a small number of people. Drug developers receive numerous benefits from the agencies to encourage the treatments for rare diseases that have unmet medical needs (7-9).

5.1 Orphan designation

The Orphan Designation Act (1983) of United States was initiated to encourage finding treatments of rare diseases. Around that decade, treatments of such diseases rarely existed and was often overlooked. Current status, inclusive of low R and D cost allocation, orphan designated drugs and diseases are one of the most expensive and profitable businesses. The definition of the work orphan drug was on the basis of not just how rare the disease was, but the rarity causing it to be neglected in the market overall. In 1984, The Food and Drug Administration (FDA) redefined orphan drug as rare diseases that affect less than 200,000 people in the United States. Research supports that orphan drug studies are more profitable than non-orphan drugs as of today (10).

6. Conclusion

Metastatic melanoma is a rare disease that affects less than 200,000 people a year, the studies for which constitute orphan and rare designated drugs. It is a novel drug that induces oxidative stress by accumulation of copper ions in the mitochondrial membrane of the cancer cells. Cuproptosis refers to cell death due to accumulation of copper ions in a matrix. This is caused by conversion of cuprous oxide ions into cupric ions. Cupric ions lead to damage in cell wall upon contact and lack of, and increase of these ions are harmful to the cancer cells. Elesclomol is an orphan designated drug used with the combination of paclitaxel and docetaxel for treatment of metastasis melanoma. Dosage and combinations of Elesclomol in phase three trails did not lead to increase in patient mortality causing it to be subjected to further investigation and clinical trials and awarding of orphan status by the Food and Drug Administration. Orphan drug studies are quite profitable and rewarding in terms of R and D. Further research into cuproptosis and Elesclomol interactions could uncover novel understanding and promising therapeutics aimed at treating melanoma (1).

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“Orphan” drugs: Good things for small populations

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1.Introduction

There is no satisfactory definition of a rare or orphan disease (OD). The World Health Organization has suggested that OD is any pathological condition that strikes fewer than 65 per 100,000 people. The USA defines a rare disorder as one that affects fewer than 2, 00,000 Americans. Australia has the limit at 5 in 10,000 individuals. A disease is deemed rare if it observe in less than 1 in 2,500 people in Japan (1). These numbers clearly relate to the population sizes of these countries. A disease may be prevalent in a particular region while being rare in another. Thalassemia is an inherited blood disorder that is rare in Northern Europe, but prevalent in Central Asia, India, and the Middle East and Mediterranean countries.

2. The Orphan Drug Act (ODA) of 1983

A rare disease is a health disorder with a low occurrence compared with common diseases, and an orphan drug is developed for the management of rare diseases. As a result, drugs for rare diseases have micromarkets that preclude researchers from recovering the money they spent on their studies.

The initial regulatory framework that fostered the creation of ODs for rare diseases was known as the Orphan Drug Act (ODA) (2). The Orphan Drug Act, was conceived and sanctioned in the United States on January 4th, 1983. At that time, treatments for such diseases were rarely developed. Before the passing of the ODA, only ten orphan drugs were accessible for patient use. The Orphan Drug Act, together with FDA policies, offers both “push” and “pull” incentives. Pull incentives include market exclusivity (3,4).

The function of the Orphan Drug Approval Law is to inspire pharmaceutical companies to enhance research for treatments of rare diseases. The FDA may award pharmaceutical manufacturers the orphan drug designation. It includes a waiver of prescription Drug User Fees, tax credits, and an extended market exclusivity period of 7 years (5). During the seven years’ marketing exclusivity period, the FDA may not award approval for the same drug for the same use but may approve a different drug for same disease (6). Since 1983, the ODA has approved a number of drugs and biologics that are useful in preventing or treating rare diseases, particularly in the fields of endocrinology, oncology, infectious disease, hematology, and neurology. A comparison of the various orphan drugs policies across the three regions is shown in Table 1.

Table 1. Comparison of the various policies on orphan drugs

Particulars	USA	Japan	Australia
Regulatory structure	Orphan Drug Act (1983)	Orphan Drug regulation (1993)	Orphan Drug Policy (1998)
Administrative authorities partnering	FDA/OOPD	MHLW/ OPSR Orphan drug division	TGA
Prevalence, for designating an Orphan status (per 10,000)	7.5	4	1.1
Marketing exclusivity period	7	10	5
Tax credit	50% of clinical studies	6 % of any sort of study + restricted to 10 % of company's corporation	No.

3. Indian perspective and initiatives by the Government

So far, only about 450 rare diseases have been recorded, and the estimated burden of rare genetic diseases is 72-96 million in India with an average time of 7 years for diagnosis. The most common among them are Thalassemia, Haemophilia, autoimmune diseases, sickle cell anaemia, Lysosomal storage disorders, primary immune-deficiency in children, Hirschsprung disease, Cystic Fibrosis, Gaucher's disease, Hemangioma, and some forms of muscular dystrophy (7).

Many of individuals afflicted with uncommon diseases increases regularly on a global scale, nations such as Canada and India ought to act decisively to address the escalating issue of orphan disease. In the meantime, the National Policy for Rare Diseases has finalized a policy and placed it on the website of the Ministry of Health and Family Welfare with a focus on the prevention of rare diseases identified by experts. The government has taken steps towards implementing legislation that will strengthen the country's healthcare system and offer assistance to many individuals who are afflicted with rare diseases.

As a response to this need, the government launched the National Policy for Rare Diseases (NPRD), 2021 in March, 2021. Under this policy, Eight Centres of Excellence (CoEs) have been identified. These are the best government tertiary health centres and their objectives are to mitigate the frequency of uncommon diseases by offering people with such diseases with access to reasonably priced treatment. The rare diseases have been recognized and classified into 3 categories as

Category 1: Disorders amenable to a single treatment

Category 2: Diseases requiring lifelong treatment with comparatively lower costs

Category 3: For which there is a convincing treatment available, however the difficulties include choosing the best patient for the best outcome, high costs, and lifetime therapy

For the diagnosis of an uncommon disease and the acquisition of funding for its treatment, patients may approach the nearest Centre of Excellence. The government is providing financial assistance of up to Rs. 50, 00,000 for the management of rare diseases in any of CoEs to the patients suffering from any category of the rare diseases mentioned in NPRD-2021. Furthermore, for genetic testing and counselling services five Nidan Kendras are now in place. Moreover, Central Technical Committee for Rare Diseases (CTCRD) under the Directorate General of Health Services has been formed under the Chairpersonship of Director General Health Services with technical experts.

4. The role of academic and research institutions in the development of drugs for rare diseases

According to the World Health Organization these conditions are strongly linked with poverty and flourish best in tropical areas. Even though many people suffer from these diseases, few medications are available on market. Historically, manufacturing companies have not shown interest in the development of drugs for rare diseases because of the poor return on investment. The government, not-for-profit organizations, pharmaceutical industry, and academic institutions, must address these issues and take initiative to provide relief from rare diseases.

Academia may face several hurdles in drug development. This appears to be attributable to various factors such as lack of resources and infrastructure, scientific guidance, deficiency of academic incentives, and the unavailability of expertise in regulatory affairs (8). Furthermore, many rare conditions are not yet linked to common diseases. Besides, challenges faced when caring for individuals with rare diseases are shown in Figure 1.

Figure 1. Challenges when caring for patient suffering from rare disease

Advanced technology in genetic science should be used for the identification of cellular and molecular pathways of orphan disease and the development of medicine. Market research, including patient population, availability, affordability, and efficacy of current treatments should be carried out to determine the potential for the development of orphan drugs. Academia can work with healthcare providers, patients, and caregivers to obtain insights into the unmet essentials in the rare disease community.

Training and experience on orphan diseases should be provided to healthcare professionals, including medical students. Furthermore, as pharmacists are credible sources of knowledge about orphan medications, they ought to be engaged with patient and parent education as well, since they are the primary caretakers (9-11). Additionally, it is crucial to offer financial, social, and psychological support systems for patients and their guardians or caretakers (12). It is important to provide the care required for patients living with orphan disease and to assist caregivers in improving the quality of life for these patients without having to compromise on their own lives (13). Academic and research institutions need to develop expertise in collaboration with multiple regulatory agencies so as to contribute to all stages of orphan drug development and disease management.

5. Conclusion

An orphan medicine is a pharmaceutical manufactured for the management of a rare disease. Since rare diseases are frequently inherited, infants, kids, and young adults are frequently impacted. A rare disease affects a small number of people, so these are often not 'adopted' by the pharmaceutical industry. Only 200 to 300 uncommon diseases have treatments available today. We believe that every individual deserves the greatest care available. The government needs to take the lead in ensuring that patients receive the best care possible and in motivating pharmaceutical companies to invest in rare disease treatment.

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Rare disorders on a global scale: Understanding the landscape


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Abstract
"Rare Disorders on a Global Scale: Understanding the Landscape" explores the complex global fabric of rare diseases, looking at their effect, prevalence, and difficulties. This sheds light on the epidemiology, obstacles to diagnosis, gaps in therapy, and the urgent need for cooperation between researchers, medical practitioners, and politicians to meet the particular requirement of people with uncommon disorders. This study intends to raise awareness, aid in early detection, and improve the standard of treatment for individuals with uncommon diseases worldwide by thoroughly examining this environment.

Keywords: Rare Disorders, Epidemiology, Diagnosis, Collaboration

1. Introduction
Beyond national and cultural borders, rare illnesses pose a complicated range of medical issues. These disorders, which are all characterized by low population prevalence, provide substantial challenges to global healthcare systems (1,2). Rare illnesses, though uncommon in and of itself, have a significant cumulative effect on millions of people worldwide. A comprehensive strategy that incorporates epidemiological surveillance, diagnostic methods, treatment plans, and cooperative efforts across other sectors is necessary to navigate the terrain of rare diseases (3,4). This introduction lays the groundwork for an investigation into the complex global dynamics surrounding rare diseases, including their consequences, prevalence, and the range of difficulties encountered by patients and healthcare professionals Through shedding light on the epidemiology of uncommon illnesses, tackling obstacles to precise diagnosis, and pinpointing deficiencies in current therapies, we emphasize the pressing necessity of cooperation between scholars, medical professionals, and decision-makers (5–7). By working together, we hope to address the special needs of people who have rare diseases, raise awareness, help with early detection, and eventually improve care quality worldwide (8)

2. Background and significance
Rare disorders are a broad category of illnesses that only afflict a small percentage of the population. Although these conditions are uncommon on their own, it is believed that 300 million people worldwide are afflicted by them collectively(9–12). These disorders are uncommon, which makes it difficult to diagnose, manage, and have access to specialized care. Furthermore, patients and their families frequently experience a sense of undervaluation and isolation due to a lack of funding and awareness for research. Comprehending the terrain of uncommon illnesses is essential for enhancing patient results and tackling unfulfilled medical requirements worldwide (11–14).

3. Objectives of the study

The objectives of this study are to give a general overview of the epidemiology of rare conditions, including information on their prevalence and geographic distribution. Examine the difficulties in identifying uncommon diseases, including concerns about awareness, instruction, and availability of genetic testing (15,16). Determine where therapeutic solutions for uncommon conditions are lacking, such as inaccessible orphan medications and restricted therapy options. Emphasize cooperative initiatives and policy ramifications, such as regulatory frameworks and multi-stakeholder engagement, for meeting the needs of people with rare illnesses (17–20). Educate about screening programs, public health initiatives, and provider education that might help raise awareness and improve early detection of rare conditions (21). Suggest recommendations for methods to raise the bar for the treatment of people with uncommon diseases, such as the use of integrated care models, palliative and supportive care, and new developments in research and innovation (22).

4. Epidemiology of rare disorders

Less than 1 in 2,000 people are usually affected with rare ailments, which are characterized by their low prevalence (23). These disorders cover a broad spectrum of illnesses, such as some malignancies and viral, autoimmune, and genetic diseases. Region-specific classification schemes may incorporate factors related to treatment choices' accessibility, severity, and frequency (24,25).

4.1. Global prevalence rates

There are large regional variations in the prevalence of rare disorders, with certain conditions being more common in particular ethnic or geographic groups. Even though they are uncommon on their own, collectively rare disorders impact a sizable percentage of the world's population, underscoring the necessity of raising awareness and stepping up research (26,27).

4.2. Geographic distribution

Rare diseases are present in populations all throughout the world, with differing rate of prevalence noted in various locales. The distribution of rare disorders within populations can be influenced by a number of factors, including genetic predisposition, environmental exposures, and availability to medical care. Comprehending the spatial arrangement of uncommon illnesses is imperative for focused screening, diagnosis, and therapeutic endeavors (27–29).

Table 1. Population data on rare diseases in South Asian countries highlights significant healthcare challenges and resource needs

Countries	Rare Diseases and Disorders Population (2,11)
Afghanistan	1530006
Bangladesh	9151081
Bhutan	44099
India	72611605

Maldives	19037
Nepal	1589670
Pakistan	10999800
Sri Lanka	1216656

Table 2. Rare diseases population data in India's union territories reveals critical healthcare challenges and resource needs

Union Territories (India)	Rare Diseases and Disorders Population
Andaman & Nicobar Islands	22797
Chandigarh	63281
Dadra & Nagar Haveli	20571
Daman & Diu	14575
Lakshadweep	3866
NTC of Delhi	1005194
Pondicherry	74668

Table 3. Rare disease population data in Indian states highlights significant healthcare challenges and resource needs

States (India)	Population (2021)	Rare Diseases and Disorders Population
Andhra Pradesh	54046659	5079932
Arunachal Pradesh	1383727	82957
Assam	35607034	1870156
Bihar	128452895	6228278
Chhattisgarh	31945023	1532412
Goa	1564760	87463
Gujarat	63872399	3623018
Haryana	30991437	1521185
Himachal Pradesh	7602350	411391
Jharkhand	38061013	1977974
Karnataka	68383140	3667842
Kerala	35699443	2003261
Madhya Pradesh	85358849	4355854
Maharashtra	123144223	6742378
Manipur	3048718	163305

Meghalaya	3366923	177840
Mizoram	1247953	65461
Nagaland	2405624	118836
Odisha	45784774	2516841
Punjab	30008595	1662254
Rajasthan	85596450	4117261
Sikkim	688263	36461
Tamil Nadu	82344607	4328337
Tripura	4222899	220262
Uttar Pradesh	240928618	11974891
Uttarakhand	11271780	607005
West Bengal	100736567	5480864

5. Challenges in diagnosis

5.1. Lack of education and awareness

Lack of awareness among patients, healthcare professionals, and the public makes diagnosing rare conditions difficult. Numerous uncommon illnesses have vague symptoms or resemble more prevalent illnesses, which can cause delays in diagnosis and incorrect diagnoses. Enhancing knowledge and instruction regarding uncommon illnesses is crucial for prompt identification and treatment (30).

5.2 Misdiagnosis and diagnostic delays

Because rare ailments are uncommon and healthcare professionals are unfamiliar with them, misdiagnosis and diagnostic delays are frequent. Before acquiring a precise diagnosis, patients may have to go through a number of tests and consultations, which might cause delays in starting the right treatment. Erroneous diagnoses can even transpire when symptoms coincide with more prevalent ailments, underscoring the significance of specialized knowledge in uncommon illnesses (31,32).

5.3 Genetic testing and molecular diagnostics

New developments in these fields have completely changed the way rare ailments are diagnosed by enabling more accurate detection of underlying genetic abnormalities. However, particularly in environments with low resources, access to genetic testing and the interpretation of results may be restricted. Furthermore, geneticists, physicians, and bioinformaticians must work together to evaluate genetic variants, which can be difficult at times (33).

6. Gaps in therapeutic interventions

6.1 Restricted treatment alternatives

Few or no specific treatments are often available for uncommon illnesses. Pharmaceutical corporations find it financially difficult to invest in medication development due to the limited patient populations. Patients with uncommon diseases may therefore have to rely on using experimental medicines or off-label usage of currently available pharmaceuticals, which carries additional dangers and unknowns (34–36).

6.2 Access to orphan drugs

For patients with rare disorders, orphan drug pharmaceuticals created especially for the treatment of uncommon disorders can offer potentially life-saving care. However, because of legal restrictions, exorbitant prices, and restricted availability in some areas, obtaining orphan medications can be difficult. The designation of a medicine as an orphan drug, which offers incentives for drug development and marketing approval, is one way to increase access to orphan drugs (37,38).

6.3 Emerging therapeutic strategies

Developing cutting-edge treatments for uncommon diseases, such as gene therapy, cell-based therapy, and targeted molecular medicines, is gaining attention despite the obstacles. These novel strategies have the potential to improve patient outcomes by targeting the underlying causes of uncommon illnesses. Nevertheless, further investigation is required to confirm their safety and effectiveness in medical environments (39–41).

7. Collaborative efforts and policy implications

7.1. Multi-stakeholder collaboration

Working together, researchers, healthcare professionals, patient advocacy organizations, business partners, and legislators can better address the complex issues of rare illnesses. Working together can make it easier to share knowledge, allocate resources, and create all-encompassing management plans for uncommon diseases (7).

7.2. Patient advocacy and support groups

Patient advocacy and support groups are essential for providing resources, raising awareness, and advocating for rare disorder needs. Along with chances for advocacy and research participation, these organizations provide patients and their families with a sense of community and support (5,11).

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7.3 Orphan drug designation and regulatory frameworks

Pharmaceutical companies are incentivized to develop therapies for uncommon ailments by regulatory frameworks like orphan drug designation. To incentivize investment in medicinal development, orphan drug classification offers market exclusivity, financial incentives, and remission of regulatory fees. Furthermore, regulatory bodies should speed the licensing procedure for orphan medications in order to provide patients with rare conditions with faster access (2,11).

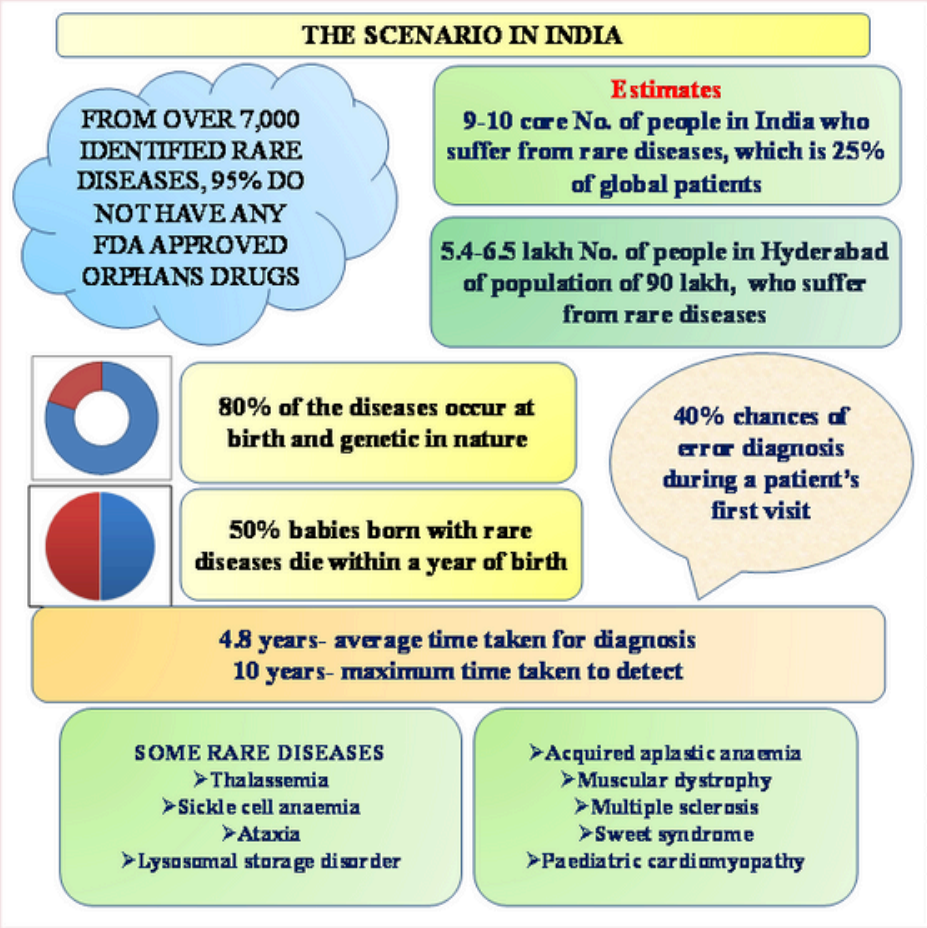

Figure 1. The scenario of rare diseases in India

7.4 Enhancing awareness and early detection

Public health campaigns have the potential to increase awareness of uncommon ailments, encourage early discovery, and lessen the stigma attached to them. To reach a variety of populations, these initiatives may include instructional materials, media outreach, neighborhood gatherings, and social media efforts (4).

7.5 Healthcare provider education

Educating healthcare professionals about uncommon illnesses improves diagnostic accuracy and the standard of care. Programs for continuing medical education, clinical guidelines, and specialized training can improve the knowledge and assurance of healthcare personnel in the management of uncommon conditions (8).

7.6. Screening and diagnostic programs

Early detection and intervention can be facilitated by putting screening and diagnostic programs for rare conditions into place. Initiatives for genetic testing, newborn screening programs, and specialized clinics can assist in identifying people who may be at risk for uncommon conditions and can give them prompt access to diagnostic services and available treatments (20).

8. Improving the standard of care

8.1. Integrative care models

By emphasizing a comprehensive approach to treatment, integrative care models can raise the bar for patients with uncommon diseases. In order to address the complex requirements of patients with rare disorders, these approaches entail the collaboration of multidisciplinary teams of healthcare providers, including specialists, primary care physicians, nurses, social workers, and allied health professionals (22).

8.2. Palliative and supportive care

These services are essential in enhancing the quality of life for people with uncommon diseases and their families. These offerings

9. Conclusion

In summary, rare disorders present a complex healthcare challenge globally, marked by low prevalence and diverse clinical manifestations. Despite these hurdles, advances in genetic testing and therapy offer hope for improved outcomes. Collaboration among stakeholders, along with increased awareness and research, is key to addressing unmet needs. Moving forward, prioritizing education, diagnosis, and treatment accessibility can enhance the lives of millions affected by rare diseases, fostering a future of innovation and support for all.

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Name: _____

Rare Diseases in India

Please unscramble the words below

1. yaoamFrgibli	a disorder characterized by widespread musculoskeletal pain
2. iaxatA	disease without coordination
3. oryucehHdlaps	an abnormal buildup of cerebrospinal fluid in the ventricles
4. osoiilAsdmy	rare disease associated with amyloid buildup
5. narlrmeBlSGradoiyunei	rare autoimmune disorder affects the nerves

Answers are on page 186

Shining light on the global network of rare diseases: Unveiling the 'rare' in not so rare


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Abstract

Orphan drugs developed to treat rare diseases represent a vital, yet often overlooked facet of modern healthcare. Rare diseases, affecting a small percentage of the population, pose significant challenges for individuals and healthcare systems. Despite their rarity, collectively, rare diseases impact millions worldwide. This review explores the interconnected realms of orphan drugs and rare diseases, defining their significance, the challenges faced by patients, and the pivotal role of orphan drugs in addressing unmet medical needs. Through legislative incentives and targeted research efforts, orphan drugs offer hope to individuals with rare diseases, providing tailored treatments and improving quality of life. Understanding and addressing the needs of this patient population are crucial steps toward achieving health equity and advancing healthcare innovation.

Keywords: Rare disease, Orphan drugs, healthcare, preventive measures, regulatory aspects

1. Introduction

Rare disease (RD) and orphan drugs (OD) are interlinked aspects of healthcare that are sometimes overlooked but are vital in enhancing the lives of individuals grappling with rare and frequently incapacitating conditions. An RD has no accepted or common definition. Its definition varies depending on the country and can be expressed as either absolute prevalence or prevalence per 10,000 people. The best definition of an RD is one that considers a nation's resources, population, and healthcare system (1). There are approximately 5,000 to 8,000 rare diseases, with about 7,000 lacking effective treatments. Overall, 300 million individuals worldwide are affected by RDs, with half of them being children, and 30 percent of this population will succumb to their condition before reaching the age of five (2). Over 5,000 medicines and biologicals are used to treat RDs (3) (Figure 1). Any medical product intended for a rare condition or one for which there is currently a lack of effective diagnostic, preventive, and therapy options is known as an OD (3). The European Medicines Agency and the United States Food and Drug Administration (USFDA) have approved a substantial number of ODs, and medications for RDs during the last 20 years (4). The proportion of medications used for oncology, infectious illness, paediatric-onset disease, and neurology has increased significantly and the prevalence of RDs can vary widely depending on the specific condition and geographic region (5) (Figure 1, 2).

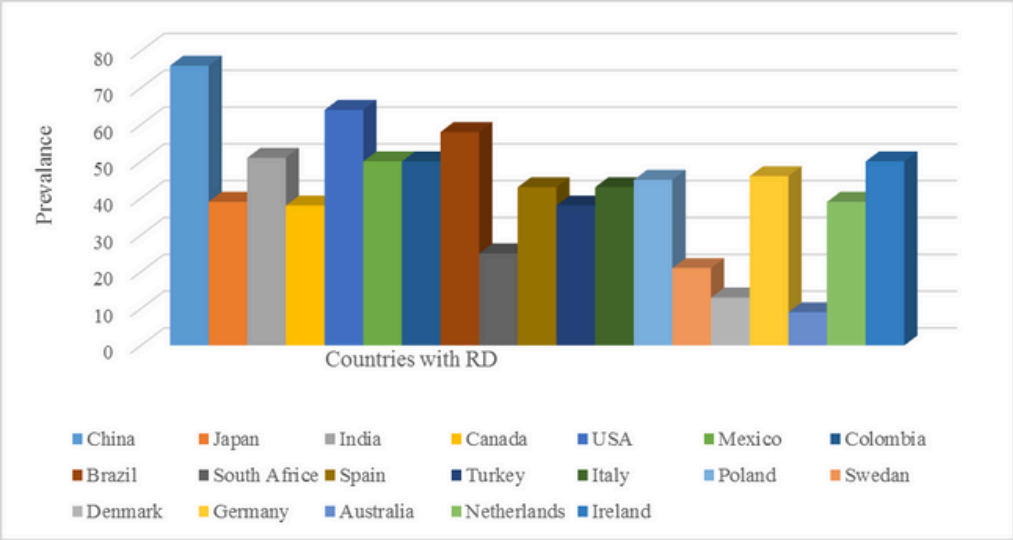

Figure 1. Data on the prevalence of RDs in different countries

Figure 2. RDs with available treatment options

Although very challenging, clinical research for orphan pharmaceuticals is exciting. It doesn't have a single feature that is particularly unique; rather, it encompasses the majority of the obstacles, including design, results, hiring, ethics, cost, probability, and predictability of success. Lack of awareness among primary care providers, inadequate screening, and inadequate diagnostic facilities are only a few of the challenges linked with early detection of RDs. Because of the low patient numbers and infrequently recovered significant expenditure, the rare occurrence of RDs frequently discourages firms from formulating novel medications. Sponsors are reluctant to design and develop these pharmaceuticals under standard marketing circumstances, leaving them "orphaned". Treatment specific to their disease has been administered to less than 10% of patients globally who suffer from RDs (3).

2. Regulatory landscape

The OD Act in the United States of America (USA) was enacted in 1983. The USA's pioneering legislation on OD was later adopted by five regions: Australia, the European Union (EU), Taiwan, and Japan. The same legislation has been developed in Singapore, Canada, and Russia, with plans to

implement their regulatory frameworks in the future. The legislation enabled the advancement of ODs for the management of RDs. The legal frameworks built in the regions have been modified according to their circumstances and needs, creating a wide range of options for the development of ODs. The USA had the highest number of orphan pharmaceuticals however, Japan and Taiwan had higher percentages of approved ODs compared to recognize ones (6).

The OD Act is designed to encourage the development of drugs, diagnostics, and vaccines to enhance treatment choices for rare illnesses by recognizing them as ODs. It is usually regarded as tremendous accomplishment in promoting research and development into RDs. These regulatory requirements can thus be considered highly effective in fostering orphan medication research (7).

The main objective of the USFDA must be to support advancements in treatments for rare illnesses by encouraging reliability, uniformity, and reasonable adaptability in the regulatory procedure within and among its review divisions (8). From the regulatory stage, the approach to developing and marketing orphan pharmaceuticals can be categorized into three separate stages (Figure 3) (9).

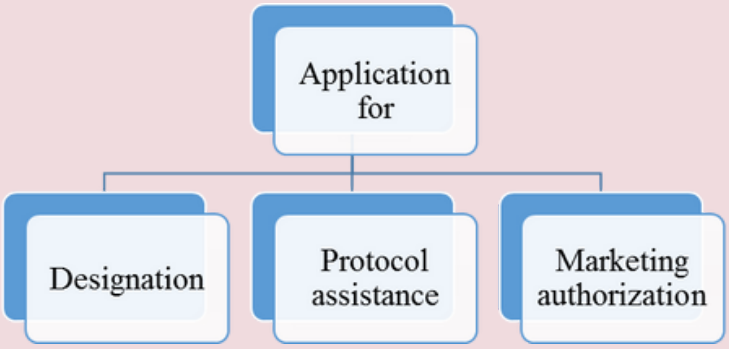

Figure 3. Stages of regulatory approach to developing and marketing OD

The EU legislation implemented the Orphan Regulation in 1999, and it was evaluated by the European Commission (EC) along with the Paediatric Regulation. Both legislations aim to tackle the scarcity of medicines accessible to the group of patients in question, and they frequently treat the same fields of therapy, as many disorders affecting children are rare. The EC has established several regulations, some of which are "Regulation (EC) No 847/2000, Regulation (EC) No 726/2004, Regulation (EC) No 2049/2005, and Regulation (EC) No 1901/2006" (10).

3. Prevention

Preventive measures for RDs can vary widely depending on the specific disease in question, its causes, risk factors, and available medical knowledge. Preventing and managing neonatal and childhood disorders are crucial aspects of RD management. (Table 1) (1).

Table 1. Preventive measures for the occurrence of RD in special population

Precautions	Implementation
Primary Prevention	Preventing the onset of the disease Eg: Avoiding pregnancy at an older age
Secondary Prevention	Avoiding the birth of affected foetus 1. Prenatal screening 2. Prenatal diagnosis by invasive testing (Chorionic Villus sampling & Aminocentesis) 3. New born screening 4. Early postnatal diagnosis & treatment

4. Drug development process (orphan drugs)

Drug development is a multifaceted, resource-intensive, and time-consuming procedure across all disease conditions. However, developing medications for RDs poses additional hurdles because of the limited number of patients, inadequate understanding of the disease, diverse clinical manifestations, and varying disease progression. Most health authorities encourage the development of orphan medications by providing a variety of incentives to firms producing treatments or diagnostics for uncommon diseases. The incentives are given as tax credits, grant funding and fee waivers (11,12). The regulatory bodies also include rapid approval, fast-track assignment, and innovative treatment categories.

The drug development process for OD can be simplified by using a checklist with the abbreviation **START** (11).

- **ST- ST**akeholder mapping
- **A**vailable information on the diseases
- Financial **R**esources
- **T**arget patient value profile

Producing strong preclinical data is a critical component of successful drug discovery. It is always ideal to employ new strategies that make the process quicker, save time and money on research, and get to market as soon as possible. The newer approaches used for preclinical studies are Induced pluripotent stem cells, Organoids and organs-on-a-chip, Modeling and simulation, and 3D cell cultures (13).

Following a satisfactory preclinical evaluation, clinical trials are carried out to determine the safety and efficacy profiles of the medication. In a typical procedure, sponsors need to submit an Investigational New Drug application, which contains the findings of the preclinical studies. In rare disease (RD) clinical trials, the low disease prevalence results in a small number of people affected by each ailment, which is exacerbated in the paediatric population of RDs (13). The small sample size allows for tailored clinical trials for orphan diseases (ODs) and RDs. This can be accomplished by multicentre trials, accessibility and incorporation of additional geographical areas, statistical trial designs (Bayesian approach), adaptive seamless designs, usage of biomarkers, and genetic and biotechnological tools (14).

5. Indian scenario

There is a dearth of information about the prevalence of several diseases that are uncommon worldwide in India. In tertiary hospitals, the cases that have been found thus far have been diagnosed. The lack of epidemiological data on the incidence and prevalence of rare diseases hinders understanding the extent of the burden these conditions impose and the formulation of a clear definition.Only a small number of illnesses that are regarded as rare worldwide have been identified in India's tertiary care facilities thus far, while the range may include 7000–8000 disorders. Under the Unique Methods of Management and Treatment of Inherited Disorders scheme, the Department of Biotechnology established Nidan Kendras (NKs) to provide genetic testing and counselling services. These NKs offer genetic testing, RD screening, and counseling (1).

6. Rare diseases team

The world envisioned by the Sustainable Development Goals includes individuals with RDs and no one is left behind. An illness does not become irrelevant or less significant than diseases that afflict millions of people just because it affects a smaller number of people (15). With this aim, a RDs Team was formed with the mission – “to help patients suffering from uncommon conditions by expediting, supporting, and facilitating the development of pharmaceutical and biologic products”

7. Rare disease day

The World RD Day, observed on the last day of February each year, is an opportunity to raise awareness of RDs that affect over 300 million people globally. The theme for 2024 was "Share your Colours," which aimed to raise awareness of the difficulties associated with having a RD. It is typical for some RD patients to have symptoms for an extended period before receiving a correct diagnosis, as there are almost 7,000 identified RDs, the majority of which do not have approved therapies. The goal of RD Day is to bring attention to and encourage support for individuals facing uncommon medical conditions worldwide. This year, February 29th, the rarest day of the year, is the final day of February, when it took place (16).

8. Success stories

Orphan medications have emerged as a key element in the management of RDs, offering hope and assistance to patients who previously had few options. Over 5000 medicines and biologicals are used to treat RDs. The proportion of medications used for oncology, infectious illness, paediatric onset disease, and neurology has increased significantly. The substantial rise in overall ODs within the last four decades indicates that there will be an upward trend in categories, resulting in increased authorization for drugs and biologics specifically developed for diagnosing, preventing, and treating RDs in the upcoming decades (17,18).

9. Challenge and future perspective

The challenges associated with OD and RD include uncertainty in the pathophysiology of the disease, lack of approved preclinical models, unavailability of benchmark reference drugs, unexpected natural origins of the disease, absence of criteria for diagnosis, endpoint selection, patient availability, and recruitment, identifying suitable sites, inadequate data, and commercialization (19,20).

The International RD Research Consortium has various goals for the future perspective (21). The goals include:

- Discovery of mechanism of RD
- Diagnosis accessibility
- Global network of undiagnosed diseases
- Educating physicians and engaging the patients
- Drug development process
- Promising advances in the development of therapies
- Engaging patients and regulatory bodies
- Evaluating the consequences of prognosis, treatment of disease
- Using tools like NIH Genetic Testing Registry and RARE Best practices

10. Conclusion

OD are medications developed for RDs that affect a small number of individuals. These drugs are granted special status by regulatory agencies to incentivize their development, such as extended market exclusivity, tax incentives, and reduced regulatory fees. The successful development and approval of OD have had a significant impact on patients with RDs by providing them with access to treatments that were previously unavailable. These drugs have improved the quality of life, increased life expectancy, and addressed unmet medical needs for individuals with RDs. Additionally, OD have led to advancements in personalized medicine and have paved the way for innovative therapies in the field of RDs.

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Orphan and rare disease: A review



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Abstract

In order to provide light on disorders that impact less percentage of the population, this review of rare and orphan diseases is an important undertaking in the medical world. Orphan diseases are characterized by their low prevalence, incomplete understanding, and frequently intricate treatment and diagnostic routes. Numerous facets of uncommon and orphan diseases are examined in this overview, including their epidemiology, challenges, available treatments, and effects on patients and healthcare systems. It emphasizes how crucial it is for researchers, medical professionals, legislators, and patient advocacy organizations to work together to increase public knowledge of these disorders, diagnose patients more accurately, and provide them with access to the right remedies. The review also covers new developments in the field of rare disease research, including precision medicine, genome sequencing, and creative therapeutic approaches that provide patients with rare and orphan diseases hope for improved prognoses and a higher standard of living.

Keywords: Prevalence, Epidemiology, Remedies, Genome sequencing, Therapeutic

1. Introduction

Rare illnesses are defined as health conditions with particularly low incidence that affect a smaller subset of the population than other prevalent diseases. A rare disease is defined by the WHO as a chronic, frequently severe illness or ailment that affects fewer than one person out of every 1000. However, each nation has its own definitions tailored to its own needs, taking into account its own resources, population, and healthcare system. A disease or illness that affects fewer than 200,000 patients in the US is considered uncommon (6.4 in 10,000 persons). According to the EU, a rare disease is one that affects a person not more than 5 out of 10,000 and is either fatal or chronically disabling. In Japan, an illness is considered uncommon if there are less than 50,000 prevalent instances (0.04%) of it nationwide (1,2). In India, an illness is considered uncommon if it affects one in 10,000 people (3). The count for the effect of rare disease for different countries are given in Table 1.

Table 1. Definition of rare disease in different countries (2)

S. No.	Country	Commonness less than per 10,000 population
1.	USA	6.4
2.	Europe	5.0
3.	Canada	5.0
4.	Japan	4.0
5.	South Korea	4.0
6.	Australia	1.0
7.	India	2.0

The Indian Rare Disease Registry was founded in 2017 by the Indian Council of Medical Research (ICMR). Encouraging patient identification through the registry will make therapy more accessible. Another advantage of the register is knowing the consequences and how the illness spreads. Along with a recent draft of the nation's first national policy dealing to rare illnesses by the Union Ministry of Health and Family Welfare, the Government of India has begun an impressive amount of work on rare diseases (4). List of organisations which deals with rare diseases in India is given in Table 2.

Table 2. Different organisations dealing with determination of rare disease (4)

S. No.	Name of Organisation	Website
1.	Metabolic errors and Rare Disease Organization of India - MERD	merdindia.com
2.	Foundation for Research on Rare Diseases and Disorders	rarediseasefoundation.org
3.	Organization for rare diseases India - ORDI	rarediseases.in
4	National Organization for Rare disorders - NORD	rarediseases.org
5.	Guardian	guardian.meragenome.com

2. Epidemiology of rare diseases (5)

Since uncommon diseases are rarely seen in the general population, their epidemiology poses special difficulties. Some key aspects of the epidemiology of rare diseases are shown in Figure 1.

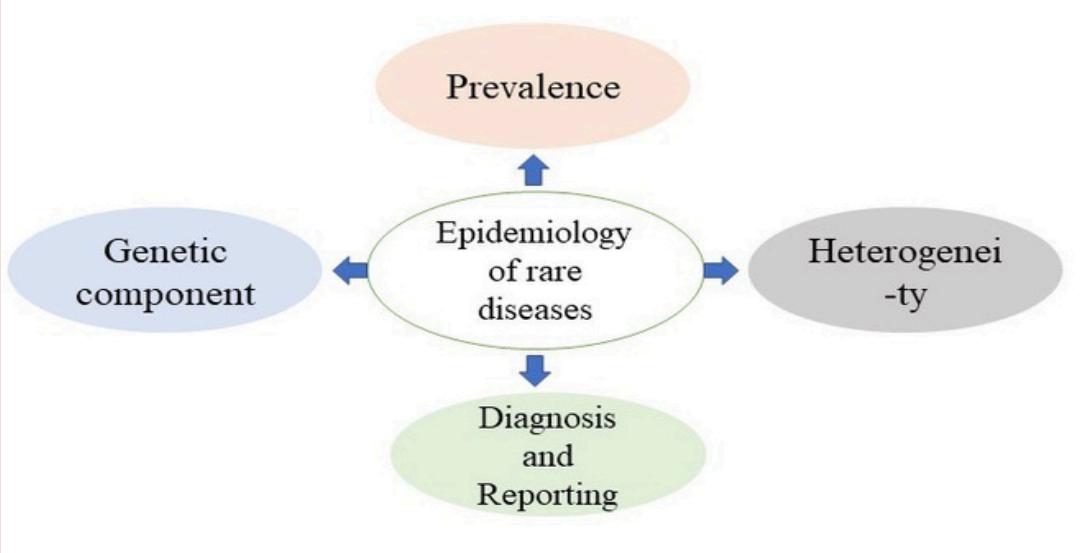

Figure 1. Epidemiology of rare diseases

2.1 Prevalence

By definition, rare illnesses are unusual. This makes it difficult to do epidemiological research on them since they might not happen frequently enough to provide sizable datasets for examination.

2.2 Heterogeneity

A wide variety of disorders, including genetic, environmental, and clinical variables, are included in the category of rare diseases. Each ailment has distinct qualities of its own. Because there might not be enough cases of any one uncommon disease to derive statistically meaningful results, this variability makes epidemiological studies more difficult to conduct.

2.3 Diagnosis and reporting

As rare diseases are not well-known to medical professionals, diagnosing them can be challenging and result in an incorrect or underdiagnosed diagnosis. Furthermore, instances can remain unreported, which would further distort epidemiological statistics.

2.4. Genetic component

Numerous rare diseases have a genetic origin, whether they are inherited or the result of random mutations. For epidemiological research to be useful in developing screening, preventative, and treatment plans, it is essential to comprehend the genetic components of uncommon illnesses.

3. Various aspects for clinical trials in rare diseases

The advancement of medication development for rare diseases can be greatly aided by using integrated mathematical analysis to the pharmacokinetic-pharmacodynamic models of selected drug candidates in order to optimize Phase III trial designs (6). This suggests that animal models and pharmacokinetic- pharmacodynamic models are required for uncommon disorders. This is the starting point for "in silico" clinical trials, which might yield information on variability (7). To select patient groups for customized therapies and to identify appropriate patient blocks for randomized trials, more statistical techniques are required to identify interactions between the therapy and

the patient's genetic background. Utilizing already-existing information to save needless clinical trials is another factor that may be utilized to suggest novel therapies for uncommon diseases. This entails searching for a medication that is currently being used clinically for a more common ailment in the unlikely event that it is also expected to be effective for the uncommon sickness (8).

4. Challenges faced in rare diseases

Rare diseases, affecting 80% of children, are exacerbated by inadequate diagnostic techniques. Next Generation Sequencing (NGS) technology enables faster identification of these diseases, allowing precise findings in 4-8 weeks, and early identification of rare disease genes (9).

India's rare diseases are poorly understood, leading to delayed diagnosis and treatment planning. Patients often lack knowledge and support, causing symptoms to wait seven years before being classified as rare. This delays drug delivery and hinders businesses from producing effective treatments (10,11). Main challenges faced by the providers are shown in Figure 2.

Figure 2. Challenges faced by the providers with rare diseases

5. Treatment for rare diseases (9,12,13)

A variety of disorders may be diagnosed via genome analysis. Gene transfer treatments are effective for patients these days. In gene therapy, viral vectors provide an efficient way to replace absent genes. Gene disruption methods such as RNA interference (RNAi), microRNA modulation, and antisense oligonucleotide can be used to modify or inhibit a disease-causing protein.

Gene-modified cell therapy can be used to alter chimeric antigen receptor (CAR) T cells in order to cure cancer. Gene editing techniques such as zinc finger (ZFN) and clustered regularly interspaced short palindromic repeats (CRISPR) are used to directly alter in-vivo and ex-vivo genes. Approved drugs for rare diseases have been steadily rising during the past 10 years.

6. Research and innovations in rare diseases

Because of advances in technology, improved collaboration among academics, and rising awareness of the particular issues encountered by people with rare disorders, research and innovation in the field of rare diseases are moving quickly forward. Sequencing technology has revolutionized genetic analysis, enabling quick and affordable diagnosis of uncommon diseases. Gene therapy, gene editing, and stem cell therapy are promising treatments. CRISPR-Cas9 and high-throughput screening are accelerating drug discovery tools. Stem cell therapy, using healthy cells from stem cells to replace organs, also shows promise. However, the business potential for rare disease therapies is low. Researchers are exploring various stem cell sources for their potential in treating uncommon illnesses (14,15).

7. Future directions and conclusion

Advances in precision medicine, gene therapy, and individualized therapies will generate a great deal of promise in rare illness research and healthcare in the future. Here is a hypothetical look at what the future may bring and some areas where more funding and policy changes may have a big impact:

7.1. Precision medicine revolution

Care for patients with uncommon diseases will continue to be revolutionized by precision medicine, which customizes medical interventions to each patient's unique needs. Clinicians will utilize molecular profiling more frequently as genomic sequencing, bioinformatics, and data analytics progress. This will enable them to discover tailored therapies based on the unique genetic mutations causing each patient's illness and make more accurate diagnoses of uncommon diseases.

7.2. Gene therapy breakthrough

Gene therapy has the potential to change the way that many uncommon genetic illnesses are treated. More advanced gene editing methods, better delivery systems, and superior safety profiles for gene therapy treatments could all be developed in the future. This might result in the approval of an increasing number of gene treatments for uncommon illnesses, providing patients with the chance to potentially cure their condition or manage it for a long time.

7.3. Personalized treatments and therapies

Personalized therapies based on each patient's distinct genetic composition, illness subtype, and clinical features will proliferate as our knowledge of uncommon diseases expands. The creation of small molecule medications, biologics, cell-based therapies, and combination medicines that target the unique biochemical pathways underlying each patient's ailment are a few examples of this.

By developing these, future advancement can help in detecting and cure of the disease symptoms before it becomes fatal to the patients.

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Advancing the potential of AI in rare disease


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1. Introduction

In recent years, the field of artificial intelligence (AI) has surged forward, catalysing transformative changes across various sectors, with healthcare being a focal point of innovation. Among the myriad areas where AI demonstrates promise, its potential in revolutionizing the diagnosis and treatment of rare diseases stands out prominently. Rare diseases, often referred to as orphan diseases, affect a small fraction of the population, yet collectively, they impact a significant number of individuals worldwide. Despite their low prevalence, these conditions present unique challenges in diagnosis and treatment due to limited awareness, scarce research, and diverse clinical presentations.

2. AI: A beacon of hope

AI technologies, particularly machine learning and deep learning algorithms, offer a beacon of hope in addressing the intricate challenges associated with rare diseases. By harnessing the power of AI to analyse vast datasets encompassing patient information, genetic data, and clinical records, healthcare providers can uncover patterns and correlations that might elude human observation. This analytical prowess enables more accurate and timely diagnoses, facilitating the initiation of appropriate treatment strategies at an earlier stage

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3. The diagnostic revolution

3.1 AI in clinical triage and diagnosis

Razzaki et al. (1) compared an AI system with human doctors in triaging and diagnosing patients using clinical vignettes. They found the AI system, trained on comprehensive EHRs and clinical notes, outperformed humans in triage and diagnosis tasks due to its proficiency in pattern recognition. However, the AI showed less accuracy in predicting hospital stay length. This underscores AI's potential to enhance clinical decision-making, especially in pattern recognition tasks, while emphasizing the need for further research to optimize its performance across healthcare settings. Similarly, AI algorithms like Aidoc (2), are employed to aid radiologists in detecting abnormalities in medical scans, including rare conditions such as Moyamoya disease or Wilson's disease, potentially enabling early intervention for improved treatment outcomes.

3.2 AI in medical image classification

In a seminal study by Esteva et al., (3) a deep convolutional neural network (CNN) demonstrated expert-level diagnostic capabilities by accurately classifying 1,29,450 clinical images across over 2,000 different diseases, comparable to 21 board-certified dermatologists. This underscores AI's potential to excel in complex medical image classification tasks, offering the promise of automated screening and triage, thereby enhancing diagnostic accessibility.

3.3 AI in pathology

Furthermore, AI extends its reach into pathology with investigations such as that by Ehteshami Bejnordi et al., (4) where multiple deep learning algorithms exhibited proficiency in detecting lymph node metastases in breast cancer using whole-slide pathology images, akin to pathologists. This convergence of AI and human expertise elevates cancer staging precision and augments patient care quality, paving the way for broader clinical validation of deep learning models in critical diagnostic domains.

4. Pioneering applications in acute care

In acute care settings like intensive care units (ICUs) and emergency departments, where timely interventions are critical, machine learning (ML) emerges as a vitality. Studies like that by Komorowski et al., (5) showcase successful ML applications in early warning systems for conditions like sepsis and acute kidney injury, highlighting the importance of integration with electronic health records (EHRs) and clinical workflows. Interdisciplinary teamwork between clinicians, data scientists, and ML experts is paramount for the effective development and deployment of ML systems in acute care environments.

4.1 Data scarcity and class imbalance

Despite these advancements, challenges persist. The study by Li et al., (6) delves into the nuances of utilizing deep learning methods for predicting rare diseases, emphasizing the hurdles posed by data scarcity due to their low prevalence, class imbalance, atypical presentations and the imperative for effective data augmentation techniques. Additionally, the necessity of interpretability and explainability in deep learning models is underscored to establish clinician trust, reducing healthcare cost and foster adoption.

5. Tackling data challenges in healthcare

Navigating the intricacies of electronic health record (EHR) data poses a significant challenge in healthcare AI. Studies by Eraslan et al., (7) and Shickel et al., (8) surveys recent advances in applying deep learning techniques such as recurrent neural networks, convolutional neural networks and autoencoders to analyse EHR data, emphasizing the importance of interpretability and trustworthiness in ensuring effective integration and acceptance of AI models. Methodological obstacles, including high dimensionality, noise, irregularity, and missingness, necessitate rigorous evaluation and collaboration between domain experts and data scientists, as highlighted by Xiao et al. (9)

6. Harnessing electronic health record data for improved patient care

Pivovarov et al., (10) delve into the analysis of temporal patterns of haemoglobin A1c (HbA1c) testing using electronic health record (EHR) data. Their study focuses on a large urban medical centre and examines the frequency and regularity of HbA1c testing over time.Findings reveal significant gaps in adherence to recommended testing intervals among patients, potentially impacting diabetes management. Factors influencing testing regularity, including patient age, gender, and comorbidities, are identified. The study underscores the value of EHR data mining and analytics in identifying care gaps and enhancing adherence to clinical guidelines, thus improving patient care outcomes.

7. Pioneering genomic discoveries

Genomics emerges as a frontier in disease diagnosis and treatment, with AI playing a pivotal role in unravelling genetic mysteries. Rostami et al., (11) review various AI techniques employed for detecting genetic diseases, showcasing their potential in gene expression analysis, variant pathogenicity prediction, and disease risk assessment and more. The integration of multi-omics data holds promises in enhancing genetic disease diagnosis and advancing personalized medicine, as emphasized by Eraslan et al.(7)

7.1 Genetic data analysis and personalized treatment

AI holds great potential for precision medicine by tailoring treatments to individual genetic profiles. By analysing genetic data, AI can uncover disease causes and guide personalized therapies. Research by Ghorbani et al., (12) emphasizes the need for collaboration among AI researchers, clinicians, and healthcare stakeholders to maximize AI's impact in clinical decision support, medical imaging, and drug discovery. Interdisciplinary efforts are crucial for developing AI solutions that benefit patients with rare diseases. For example, IBM Watson for Genomics (13) analyses genetic data to find targeted treatments for conditions like cystic fibrosis and Duchenne muscular dystrophy

7.2 Epigenetic therapies in personalized medicine

In the similar vein, Feinberg (14) highlights the pivotal role of epigenetics in disease prevention and management, shedding light on how epigenetic mechanisms influence disease susceptibility, progression, and treatment response. This underscores the potential of epigenetic therapies in personalized medicine, offering tailored interventions based on individual epigenetic profiles. Additionally, Guinney et al., (15) contribute to precision oncology by identifying distinct molecular subtypes of colorectal cancer, paving the way for subtype-specific targeted therapies and emphasizing the integration of multi-omics data for comprehensive patient stratification.

8. Navigating challenges with precision

Miotto et al., (16) provide a comprehensive overview of the evolving landscape of deep learning applications within healthcare. They highlight the potential of deep learning to extract valuable insights from complex healthcare data, including medical imaging, electronic health records (EHRs), and genomics. The paper emphasizes the importance of collaboration between clinicians, data scientists, and domain experts to address challenges such as data quality, privacy concerns, and the critical need for interpretability and transparency in healthcare applications of deep learning. Additionally, future opportunities and research directions, such as transfer learning, federated learning, and integration of multi-modal data sources, are discussed to advance deep learning's impact on healthcare.

9. Addressing behavioural health challenges

Beyond genetics, AI extends its reach into understanding behavioural health challenges. Yip et al., (17) explores the relationship between childhood and adult trauma experiences and behavioural health problems among incarcerated individuals, shedding light on the profound impact of trauma on mental health outcomes. Their findings underscore the importance of trauma-informed care in both correctional and community-based treatment settings.

10. Unravelling metabolomics and cancer complexity

10.1 Metabolic alterations and obesity

Cirulli et al., (18) elucidates the metabolic alterations associated with obesity, providing valuable insights into personalized risk assessment and intervention strategies for obesity-related conditions such as diabetes, cardiovascular diseases, and cancer. Their findings highlight the reversibility of metabolic perturbations with weight loss, offering hope for targeted interventions.

10.2 Cancer biology and precision medicine

Furthermore, Hanahan and Weinberg (19) expanded cancer biology knowledge by identifying new hallmarks, emphasizing their importance in targeted cancer therapies. Personalized approaches, informed by metabolomics and the tumour microenvironment, hold promise in combating cancer. Hyman et al., (20) showcased successful targeted therapy in non-melanoma cancers with BRAF V600 mutations, illustrating precision medicine's potential across tumour types. AI reveals cancer's complexity and offers precision medicine avenues. Mayr and Bartel (21) uncovered novel cancer progression mechanisms, suggesting new therapeutic targets. The Cancer Genome Atlas Network (22) revealed genomic heterogeneity in head and neck squamous cell carcinomas, informing tailored precision oncology strategies.

11. Ethical Guidelines and Regulatory Compliance for AI in Healthcare

In the rapidly evolving landscape of healthcare technology, ethical considerations emerge as a pivotal concern. Topol (23) advocates for "high-performance medicine," stressing the harmonious collaboration between AI and human intelligence, highlighting the imperative for responsible AI development and implementation. Anagnostou et al., (24) underscore the paramount importance of human-AI collaboration, particularly in leveraging genomic sequencing and personalized medicine to advance disease prevention and wellness.

Ethical integration of AI into healthcare is emphasized by the World Health Organization (25), offering comprehensive guidelines that prioritize transparency, fairness, accountability, and privacy protection. These principles, accessible on the WHO website, aim to instil trust among patients, healthcare providers, and regulatory bodies. Additionally, the American Medical Association (AMA) contributes tailored ethical guidelines for healthcare practitioners and patients.

Regulatory bodies such as the FDA and EMA play a crucial role in ensuring the ethical use of AI in healthcare. The FDA's guidance on "Artificial Intelligence and Machine Learning in Software as a Medical Device" (2021) and similar efforts by the EMA focus on ethical standards and patient safety, aiming to establish clear regulatory frameworks that uphold ethical practices in AI technology deployment within medical settings (26).

12. Other real-world examples of AI applications

Real-world examples of AI applications in healthcare extend beyond rare diseases:

- **12.1 Drug discovery and development:** BenevolentAI (27) harnesses AI for swift drug discovery, analysing biomedical data to pinpoint potential drug candidates and forecast their effectiveness and safety across diseases. Atomwise (28) and Insilico Medicine (29) also leverage AI algorithms to predict molecule activity and screen vast compound databases, focusing on rare diseases like ALS or Huntington's.
- **12.2 Remote patient monitoring:** Ling and Xu (30) discuss AI-powered wearable devices and remote monitoring systems, enabling continuous tracking of patient health parameters. These devices equipped with AI algorithms detect early signs of deterioration in chronic conditions like heart disease or diabetes, facilitating timely intervention.
- **12.3 Natural language processing (NLP) in healthcare:** Linguamatics (31) develops NLP solutions to extract insights from unstructured healthcare data, including clinical notes and patient transcripts. These solutions aid healthcare providers in extracting relevant information to support clinical decision-making and research.
- **12.4 Collaborative research networks:** AI fosters collaborative research and data-sharing among healthcare institutions, researchers, and pharmaceutical companies to advance rare disease research. Projects like RDCA-DAP (32) use AI to integrate and analyse diverse data, speeding up the discovery of rare disease treatments.

13. Emerging trends in AI technology

Emerging trends in AI technology include Explainable AI (XAI), which emphasizes transparency and interpretability of AI algorithms. Lundberg and Lee's research (33) highlights methods like LIME and SHAP to aid clinicians in understanding AI-driven clinical decisions. AI-driven Clinical Trials,

exemplified by Deep 6 AI (34), optimize patient recruitment and predict outcomes, enhancing trial success rates. Personalized Health Assistants, like those offered by Ada Health (35) and Babylon Health, provide tailored health recommendations and support through AI-powered chatbots, improving access to healthcare services remotely. These advancements showcase AI's potential to revolutionize healthcare delivery and patient outcomes.

14. Conclusion

As AI continues to evolve, the potential for enhancing rare disease diagnosis and treatment grows exponentially. By combining AI's analytical prowess with the expertise of healthcare professionals, we can unlock new insights, develop innovative therapies, and improve outcomes for patients with rare diseases. Through collaborative efforts and a commitment to ethical AI practices, we can propel the field of rare disease medicine forward, offering hope to individuals facing these challenging conditions.

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A brief review on *Gilles de la Tourette* syndrome: A rare disease

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Abstract

Tourette syndrome is a rare disease with various physical and vocal tics that begin in childhood, last at least a year, and are not caused by other medical conditions or medicines. Tics can be easily identified using clinical diagnostic criteria and their distinct look and characteristics. In this article we are going to see the etiology, factors due to which the Tourette syndrome occurs and the ways to treat this syndrome.

1 Introduction

Despite rare diseases afflicting a tiny number of people (less than 1 in 2000 in any WHO area), there are over 7000 different forms of rare diseases. The load that exists on a global scale is considerable. Currently, almost 300 million people have uncommon illnesses. Individuals in low- and middle-income nations regularly face neglect and marginalization (1). Approximately 80% of rare diseases have a genetic basis, with over 70% presenting in childhood. Approximately 95% of rare diseases do not have authorized therapies, with an average diagnostic time of 4.8 years. Additionally, approximately 30% of children with rare diseases dies before reaching the age of five (2). In 2021, the UN adopted the first resolution to address the issues faced by individuals with rare diseases and their families (3,4). The resolution encourages Member States to offer reliable and reasonably priced health services, especially at the primary care level.

2. Types of rare diseases

2.1 Genetic disorders: Many rare diseases are caused by genetic mutations or abnormalities. These can include disorders like Duchenne muscular dystrophy, Huntington's disease and cystic fibrosis.

2.2 Autoimmune diseases: Some autoimmune diseases are rare and can affect various organs or systems in the body. Examples include systemic lupus erythematosus (SLE) and autoimmune hemolytic anemia.

2.3 Metabolic disorders: These are rare conditions that involve problems with metabolism, such as phenylketonuria (PKU) or Gaucher disease.

2.4 Rare cancers: Certain types of cancer are considered rare because they occur infrequently compared to more common forms like lung or breast cancer. Examples include mesothelioma and some types of paediatric cancers.

2.5 Neurological disorders: There are various rare neurological conditions, like amyotrophic lateral sclerosis (ALS), Huntington's disease and Rett syndrome.

2.6 Rare infectious diseases: Some infectious diseases are rare, either due to their geographic distribution or the nature of the pathogen. Examples include Chagas disease and Ebola virus disease (1).

2.7 Rare paediatric diseases: Many rare diseases affect children. These can range from rare genetic disorders to specific paediatric cancers.

2.8 Rare haematological diseases: Certain blood disorders fall under the category of rare diseases, such as aplastic anaemia or haemophagocytic lymphohistiocytosis (HLH).

2.9 Rare respiratory diseases: Conditions like pulmonary arterial hypertension (PAH) or idiopathic pulmonary fibrosis (IPF) are considered rare diseases affecting the lungs.

2.10 Rare rheumatological diseases: Some rare diseases affect the joints and connective tissues, such as Behçet's disease or relapsing polychondritis (5).

It's vital to take note that there are thousands of rare diseases, and new ones are continually being discovered. The impact of rare diseases on individuals and families can be profound due to the challenges in diagnosis, limited treatment options, and often lack of awareness and research (6). Efforts in rare disease research, advocacy, and support aim to improve the lives of those affected by these conditions (7,8). Table 1, explains the prevalence of rare diseases throughout the world.

Table 1. Prevalence and types of action towards rare diseases in different countries

S No.	Criterion	United states	UK	China	Japan	Taiwan
1.	Criterion for prevalence of rare diseases (%)	0.75	0.5	0.11	0.4	0.1
2.	Affected population	25-30 million	27-36 million	27-36 million	NA	More than 2000
3.	Administrative bodies involved	FDA/OOPD	EMA/COMP	TGA	MHLW	DOH
4.	Legal framework	Orphan Drug Act (1983), Rare Diseases Act of (2002)	Regulation (EC) No.141/2000 (1999)	Orphan Drug Policy (1997)	Revised orphan drug regulations (1993)	Rare Diseases Control and Orphan Drug Act
5.	Financial subsidies	Government grant for clinical research	Frame work programs plus national measures	NA	Government grant for research	Government grants and awards from the central competent authority
6.	Market exclusivity (years)	7	10	5	10	10

7.	Tax credits	Upto 50% for clinical expenses	Managed by member states	Not applicable	15% tax credits	Not applicable
8..	Protocol assistance	Yes	Yes	Yes	Yes	Yes
9.	Administrative bodies involved	Market driven	Depending on member states	Same as other drugs	Price negotiation	Not applicable
10.	Medical expense reimbursement	Yes	Yes	Yes	Yes	70% for patients, upto 100%for low income family

3. Tourette syndrome

Tourette syndrome, initially defined by *Gilles de la Tourette* in 1885, is a hyperkinetic mobility condition characterized by many motor tics and at least one phonic tic that continues for more than a year after start, but not always concurrently. Tics must start before age 18 and not be caused by other circumstances. A tic is a repeating muscular action or vocal sound that lacks rhythm. Individuals with Tourette syndrome endure varying degrees of disability and tics, which may change over time. Tics can induce muscular exhaustion and pain from repeated contractions and motions(9,10).

3.1 Etiology

The exact etiology of Tourette syndrome (TS) It is not completely understood, although it is thought to entail a mix of environmental, genetic and neurological influences(10). Here are few key aspects of TS etiology.

3.2. Genetic factors

Tourette syndrome has a strong genetic component. Studies have shown that TS runs in families, with identical twins having a higher concordance rate than fraternal twins. Multiple genes are thought to contribute to the genesis of TS, with each likely having a little influence. However, no one gene has yet been proven to be the sole cause of TS.

3.3 Neurobiological factors

Dysregulation of neurotransmitters TS is linked to disorders in neurotransmitter systems, namely serotonin, dopamine, and Neurobiological Factors: Dysregulation of neurotransmitters TS is linked to disorders in neurotransmitter systems, namely serotonin, dopamine, and norepinephrine. Dysfunction in these systems may lead to the development of tics and related symptoms. Dysfunction in these systems may lead to the development of tics and related symptoms.

3.4 Changes in brain structure and function

Neuroimaging studies have identified abnormalities in the structure and function of certain brain areas in TS patients, including the frontal cortex, basal ganglia and limbic system. These regions are important in motor control, inhibition, and emotional regulation, which suggests that TS symptoms may be caused by anomalies in these circuits.

3.5 Environmental factors

While inherited factors play an essential role, environmental circumstances can also impact the development or progression of TS symptoms. Some occurrences have been linked to environmental factors such as prenatal and neonatal problems, mothers who smoke during pregnancy and access to specific chemicals or viruses.

3.6 Immune system dysfunction

There is growing evidence that immune system problems and inflammatory responses can add to the pathophysiology of TS. Autoimmune processes and neuroinflammation have been suggested as possible contributing causes.

3.7. Psychosocial factors

Anxiety, stress, and emotional discomfort can all impact the intensity and frequency of tics in people with TS. Stressful life events or social demands may worsen symptoms, but supportive surroundings and good coping skills might help alleviate them.

Recent research reveals that tic disorders, such as Tourette syndrome, may be genetic, while this is still considered hypothesis. Some evidence indicates that serotonin may have a role in TS-related tics, while the specific mechanism is uncertain. Small sample sizes and concurrent obsessive-compulsive disorder have made it difficult to confirm a role for serotonin in this concept. Dopaminergic activity appears to influence the pathophysiology of the condition, although further data is needed. Tics associated with TS have been connected to premonitory desire. These uncomfortable feelings of stress arise before and are temporarily relieved after a tic. Although premonitory wants are an important component of tics, their physiological source is unclear. Neuroimaging demonstrates that the motor circuit in TS is identical to that in normal voluntary behaviours. Currently, abnormal activity in these areas is thought to be causal. A study of children with TS at the Danish National Tourette Clinic found that the severity of tics, ADHD, and OCD in childhood was significantly related to the severity scores in early adulthood. In the same cohort, 18% of individuals over 16 had no tics, 60% had minimal or mild tics, and 22% had moderate to severe tics, showing that tics diminish with age(11).

3.8 Treatment for Tourette syndrome:

Treatment of TS, a neurological illness characterised by recurrent, involuntary movements and vocalisations known as tics, can vary depending on the severity of symptoms and their impact on daily life. While there is no cure for Tourette syndrome, various approaches can help manage symptoms effectively. Here are common treatment options(12):

3.8.1 Behavioural therapies

Comprehensive Behavioural Intervention for Tics (CBIT) helps persons with TS get more conscious of their tics and learn how to regulate or suppress them. CBIT might include habit reversal training, that involves identifying tic triggers and replacing them with alternate movements or actions.

3.8.2 Cognitive behavioural therapy (CBT)

It can assist patients with Tourette syndrome manage stress and anxiety, potentially reducing the frequency and intensity of tics.

3.8.3 Medications

- Neuroleptics or antipsychotics: Haloperidol, pimozide, risperidone, or aripiprazole can reduce tics by affecting dopamine levels in the brain. However, they may cause serious adverse effects and must be closely monitored. Alpha-2 Adrenergic Agonists: Guanfacine or Clonidine can be used to treat tics, ADHD, and impulse control concerns.
- Botulinum Toxin (Botox) injections help alleviate motor tics by targeting particular muscle groups. This therapy is most typically used for people who have severe and incapacitating tics.

3.8.4 Deep brain stimulation (DBS)

This surgical therapy involves implanting electrodes in specific areas of the brain to regulate abnormal nerve impulses that cause tics. DBS is explored when previous therapies have been ineffective or poorly tolerated.

3.8.5 Supportive therapies

- Occupational Therapy: Occupational therapy can assist persons with Tourette syndrome in developing coping strategies and improving motor abilities.
- Speech therapy can help manage vocal tics and enhance communication skills.
- Education and support: Healthcare experts, support groups, and advocacy organisations may help individuals and families cope with Tourette syndrome(13).

People with Tourette syndrome should engage together with their healthcare professionals to build a comprehensive treatment plan to meet their unique requirements and concerns. Treatment strategies may evolve over time based on changes in symptoms and individual response to therapies.

4. Conclusion

To summarise, uncommon illnesses represent a significant public health concern and a challenge to medical care. In recent years, there has been significant progress in several regions of Asia, notably Japan, South Korea, and Taiwan, with the passage of legislation and subsequent regulation of rare illnesses and orphan pharmaceuticals. Tourette syndrome is a neuropsychiatric condition that causes physical and vocal tics in children and can lead to concomitant psychopathology in up to 90% of cases. Diagnosing tics can be difficult due to their shifting course, variable symptomatology, and co-occurring mental and movement disorders. However, diagnostic criteria and crucial clinical factors can consistently identify tics from their imitators. ADHD and obsessive-compulsive disorder are common comorbidities that can worsen disability and lower quality of life. To prioritize treatment goals, patients should undergo a comprehensive neuropsychiatric assessment, including collateral history and severity scales. Most Tourette syndrome patients enjoy reduced tic intensity during adolescence. However, a minority of patients continue to suffer tics in adulthood, leading to greater rates of anxiety, low self-esteem, unemployment, and lower socioeconomic position. More study is needed to understand the influence of motor and mental symptoms on function and quality of life in people with Tourette syndrome across time.

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Nephrotic syndrome: Rare chronic kidney disease

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1. Introduction

The rare disease "nephrotic syndrome" refers to a kidney illness that causes your body to discharge an excessive amount of protein in urine. Nephrons, which are around a million filtering units, make up the kidneys. Each nephron consists of a tubule and a filter known as a glomerulus. The tubule replenishes the blood with necessary chemicals and eliminates surplus water and wastes, resulting in urine, while the glomerulus filters the blood. Damage to the glomeruli causes excessive amounts of protein to seep from the circulation into the urine, which is often the cause of nephrotic syndrome (1). The term "nephrotic-range proteinuria" refers to the loss of protein up tothree grams or more through urine in a period of 24-houror the presence of two grams of protein for every gram of urine creatinine in a single urine sample (2).

The English physician Richard Bright initially characterized nephrotic syndrome in his landmark 1827 publication "Reports of Medical Cases". Understanding the condition was made possible by Bright's documentation of the clinical signs of proteinuria, edema, and hypoalbuminemia in renal disease patients (3). Researchers like Friedrich Theodor von Frerichs and William Osler contributed to the understanding of the pathological alterations and clinical characteristics linked to nephrotic syndrome in the late 19th and early 20th centuries. Their work improved our understanding of the underlying causes of nephrotic syndrome and helped distinguish it from other kidney diseases (4).

2. Pathophysiology

Damage to the kidney's glomeruli, which are in charge of removing waste and surplus chemicals from the blood while holding onto vital proteins like albumin, is part of the pathophysiology of nephrotic syndrome. Proteinuria results from the glomeruli becoming too porous in this disease, which permits proteins like albumin to seep into the urine. Nephrotic syndrome in children can be caused by a number of underlying disorders, the most prevalent of which is minimal change disease. Additional reasons include membranous nephropathy, membranoproliferative glomerulonephritis, and focal segmental glomerulosclerosis. Its development may be influenced by immunological factors, genetic predisposition, infections, and environmental causes (5,6).

2.1 Characteristics of nephrotic syndrome

Nephrotic syndrome is a kidney disorder characterized by the following key features (7):

- **Heavy proteinuria**: The condition known as "heavy proteinuria" occurs when there is an excessively high level of protein in the urine, usually more than 3.5 grams per day.

- **Hypoalbuminemia:**Low albumin levels in the blood, often less than 3 grams per deciliter are known as hypoalbuminemia.
- **Edema:** Swelling brought on by fluid retention, especially in the legs, ankles, and eye area.
- **Hyperlipidemia**:Increased blood lipid (fat) levels, such as those of cholesterol and triglycerides, are known as hyperlipidemia.

2.2 Classification

Nephrotic syndrome can be categorized according to a number of factors, such as clinical presentation, histology, and etiology. Based on these variables, the following categorization of nephrotic syndrome exists (8).

2.2.1 Etiological classification

Nephrotic syndrome that develops without a known underlying cause is referred to as

- **Primary nephrotic syndrome:** The primary nephrotic syndrome including various conditions like focal segmental glomerulosclerosis (FSGS), membranousnephropathy and minimal change disease.
- **Secondary nephrotic syndrome:** An underlying systemic illness or condition causes the syndrome to develop in secondary nephrotic syndrome cases. Amyloidosis, diabetes mellitus, systemic lupus erythematosus (SLE), and certain infections are common secondary causes.

2.2.2 Histopathological classification

- **Minimal change disease (MCD):** Under optical microscopy, no alterations are observed in any Change Disease (MCD), however under electron microscopy, there is considerable podocyte foot process effacement.
- **Focal segmental glomerulosclerosis (FSGS):** FSGS causes nephrotic syndrome and proteinuria by sclerosis and scarring some but not all glomeruli.
- **Membranous nephropathy (MN):** The thickening of the glomerular basement membrane as a result of immune complex deposition is a characteristic of Membranous Nephropathy (MN).
- **Membranoproliferative glomerulonephritis (MPGN):** Thickening of the glomerular basement membrane as a result of both cellular proliferation and the deposition of immune complexes.

2.2.3 Clinical classification

- **Steroid-responsive nephrotic syndrome:** Nephrotic syndrome that responds effectively to corticosteroid therapy is known as "steroid-responsive nephrotic syndrome," which is usually observed in minimal change illness.
- **Steroid-resistant nephrotic syndrome:** Nephrotic syndrome, which can arise in FSGS and other disorders, that is unresponsive to corticosteroid treatment.
- **Relapsing nephrotic syndrome:** Nephrotic syndrome relapsing is characterized by intervals of remission followed by a return of symptoms.
- **Persistent nephrotic syndrome:** Nephrotic syndrome that remains untreated and does not go into remission is known as persistent nephrotic syndrome.

2.2.4 Genetic classification

Mutations in genes encoding proteins involved in podocyte organization and function are among the genetically based types of nephrotic syndrome. Examples include congenital nephrotic syndrome-related mutations in the NPHS1 and NPHS2 genes.

2.2.5 Age-related classification

Certain age groups are more likely to have certain kinds of nephrotic syndrome. For instance, membranous nephropathy is more common in adults, although minimum change disease is more frequently observed in children.

2.2.6 Health care professionals use various terms to understand nephrotic syndrome in children

- Congenital nephrotic syndrome is present within birth to 3 months
- Infantile nephrotic syndrome is present within 3 to 12 months
- Childhood nephrotic syndrome is present within 12 months or older

3. Incidence and prevalence

3.1 Incidence

Nephrotic syndrome is thought to affect 2–7 out of every 100,000 children globally each year. Although the occurrence in adults is less certain, it is often lower than in children.

3.2 Prevalence

Nephrotic syndrome is thought to affect around 16 out of every 100,000 children in Western nations. Adult prevalence is less certain and varies based on the demographic and underlying reason under investigation. Nephrotic syndrome affects less than 5 out of every 100,000 children worldwide on average each year. A significant chronic illness that affects children is nephrotic syndrome. Every year almost two to seven new instances out of every 100,000 children under the age of eighteen were affecting by nephrotic syndrome (9-11).

Srivastava R N et al. (1975) studied and a major renal cause was found in 195 (96%), of which 77% were males, of the 206 Indian children with nephrotic syndrome analysed clinic-pathologically. Before the age of five, the condition manifested in 126 children (sixty-six boys and thirty girls). Three months to sixteen years following the beginning of nephrotic syndrome, renal biopsies were performed on 85 of the 150 patients (77%), and the results revealed mild abnormalities. The conditions that classified renal histological abnormalities in 45 instances were Membranous 3, focal segmental glomerulosclerosis 9, focal global glomerulosclerosis 2, advanced nonspecific 8, and moderate proliferative 9. Clearance of proteinuria with corticosteroid therapy was mostly limited to patients with mild or moderate renal histological alterations. According to our research, Indian children's idiopathic nephrotic syndrome pattern is comparable to that of Western nations (12).

4. Symptoms and diagnosis

4.1 Symptoms (7)

- Severe Swelling (Edema): Especially around the eyes, legs, and feet.
- Foamy Urine: Due to high levels of protein in the urine.
- Weight Gain: From fluid retention.
- Fatigue: Due to loss of protein and overall health decline.
- Loss of Appetite

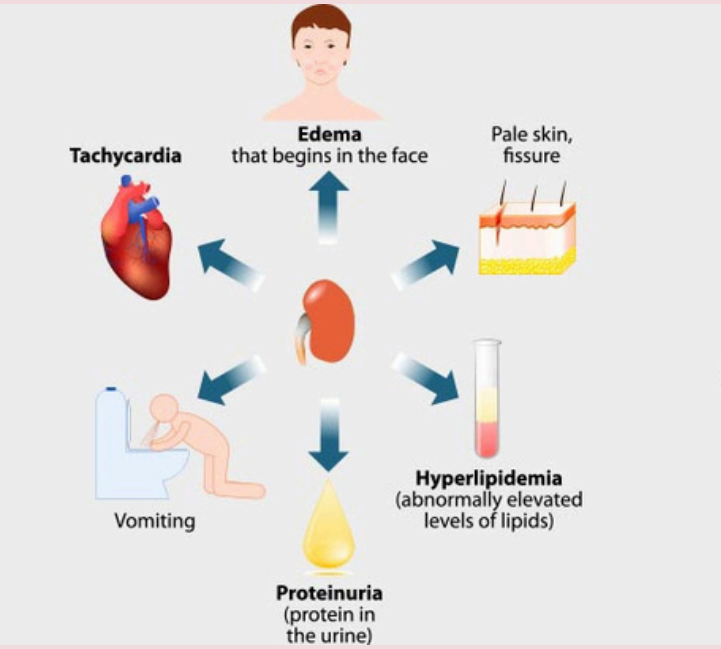

Figure1. Symptoms of nephrotic syndrome (7)

4.2 Diagnosis (7,13)

- Urine Tests: To detect high levels of protein and assess kidney function.
- Blood Tests: To check levels of albumin, cholesterol, and kidney function markers.
- Kidney Biopsy: Sometimes performed to determine the specific cause of nephrotic syndrome.

5. Treatment and management

Nephrotic syndrome treatment consists of treating the underlying cause, controlling symptoms, and preventing consequences. Common approaches include (7,13):

5.1 Medications

- Corticosteroids and Immunosuppressant: To reduce inflammation and immune response, particularly in primary nephrotic syndrome.
- Diuretics: To reduce fluid buildup and swelling.
- ACE Inhibitors or ARBs: To reduce blood pressure and protein loss in the urine.
- Statins: To manage high cholesterol levels

5.2 Dietary changes

- Low Sodium Diet: To reduce swelling.
- Low Protein Diet: Sometimes recommended to decrease protein loss through urine.
- Low Fat Diet: To manage cholesterol levels.

6. Complications

If not properly managed, nephrotic syndrome can lead to several complications, such as (7):

- Infections: Increased susceptibility due to loss of immunoglobulin in the urine.
- Blood Clots: Due to loss of proteins that prevent clotting.
- Chronic Kidney Disease: Potential progression to kidney failure.
- Acute Kidney Injury: Sudden decline in kidney function.

7. Prognosis

The prognosis for nephrotic syndrome varies depending on their cause and response to treatment. Some cases, particularly in children with minimal change disease, respond well to treatment and may go into remission. Other forms, such as FSGS or membranous nephropathy, may have a more chronic course and risk of progressing to chronic kidney disease. Regular follow-up with a healthcare provider is essential for monitoring and managing the condition effectively (11).

8. Future aspects

The future of nephrotic syndrome seems promising as researchers investigate new medicines, diagnostic tools, and approaches to customized care. The interdisciplinary nature of nephrology research and the cooperative efforts of clinicians, scientists, and industry partners in advancing the understanding and management of nephrotic syndrome are highlighted by future perspectives such as regulatory tolerance induction, precision medicine, biologic therapies, stem cell therapy, nanomedicine, biomarker discovery, artificial intelligence and machine learning, telemedicine, and remote monitoring. Sustained funding for research, innovation, and translational medicine is necessary to fully use these novel treatment approaches and enhance nephrotic syndrome patient outcomes.

9. Conclusion

In order to sum up, fighting orphan and rare diseases necessitates concerted efforts to overcome challenges and benefit from new advancements in collaboration and research. Important challenges involve the necessity for continuous cooperation and funding in addition to the developments in genomics and precision medicine. Limited resources and uneven access are further issues. It is essential that we put out a call to action for increased awareness and support, pleading with interested parties to demand improved funding for healthcare access, education, and research. Working together and prioritising the needs of persons with rare and orphan diseases can greatly enhance results and standard of life.

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Global perspectives on rare and orphan diseases: Prevalence, impact, and diagnostic challenges

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Abstract

Rare and orphan diseases affect a minor segment of the population but represent a significant global health challenge due to their diversity and the specialized care required. This study offers a comprehensive global perspective by examining the prevalence, impact, and policy responses concerning rare and orphan diseases. Utilizing a mixed-method approach, data was gathered from global health databases and interviews with healthcare professionals and policymakers. The findings underscore the gaps in current healthcare systems and highlight successful strategies implemented in various countries. The study continues with a discussion of the implications of the disease for public health policy and recommendations for future research to meet the unresolved requirements of patients with orphan and rare diseases.

Keywords: Rare diseases, Orphan diseases, Epidemiology impact, Diagnostic challenges.

1. Introduction

As stated by the World Health Organization, orphan diseases are group of illnesses with an estimated incidence of fewer than 6.5 to 10 instances per 10,000 people. Because these illnesses are incredibly rare and reported globally rarely, they have not received much public attention (1).

Orphan diseases" are ailments that are considered "neglected," meaning that there is a shortage of viable remedies due to a lack of research on diagnosis and therapy. The concepts of orphan and uncommon diseases differ, yet, in that some common diseases are nonetheless deemed orphan since they largely strike low-income countries and there may be limited financial incentives to explore them (2). Rare diseases impact around 6% of the population worldwide (3). Because of their rarity, 25% of patients have to wait 5 to 30 years for a diagnosis. Approximately 5000 to 8000 RDs have been determined around the world (4), with varying risk factors, origins, signs, remedies, and geographical distribution (5).

Despite their diverse characteristics, they all have one thing in common: they are rare, with patients confronting similar obstacles in detection, therapy, and management. Doctors in general and clinicians in local healthcare facilities may lack competence with rare diseases, resulting in a delay in detection and referred to more specialized institutes. According to a European survey, it required 5 to 30 years for nearly one-quarter of individuals with rare disorders to receive a confirmed diagnosis after experiencing early symptoms. Of these, 40% had either no diagnosis

at all or an incorrect one. Many individuals had to meet with multiple doctors before receiving their final diagnosis. The resulting delays were primarily caused by clinicians' unfamiliarity with rare disorders (6,7). Long-lasting symptoms, the advancement of the illness, lower quality of life, needless hospital stays and interventions, ineffective pharmaceutical and non-pharmacological treatment, and possibly even a higher death rate can all be consequences of a delayed diagnosis (8).

The absence of uniform statistical information across geographies and populations and the rarity of the illnesses (low prevalence) hinders clinical trial implementation and data collection in the actual world. This, in turn, impedes the development of safe and novel treatments (9). Despite significant national differences, RD treatment is still a global topic that frequently affects patients, their families, and caregivers. Patients bear a huge emotional, financial, and social burden. Patients find it difficult to navigate the healthcare system, even in industrialized nations with more developed policies, funding, and professional guidelines for rare diseases. This results in notable differences in the quality of patient care and accessibility to treatment between different socioeconomic groups and communities (10).

2. Epidemiology impact

An estimated 350-475 million people worldwide are predicted to be affected by RDs, with children making up about 50% of those affected in a 2020 World Economic Forum report. As RDs are frequently underdiagnosed, several nations only have prevalence estimates (11). Figure 1 depicts an estimated number of persons affected by Rare Diseases across different locales

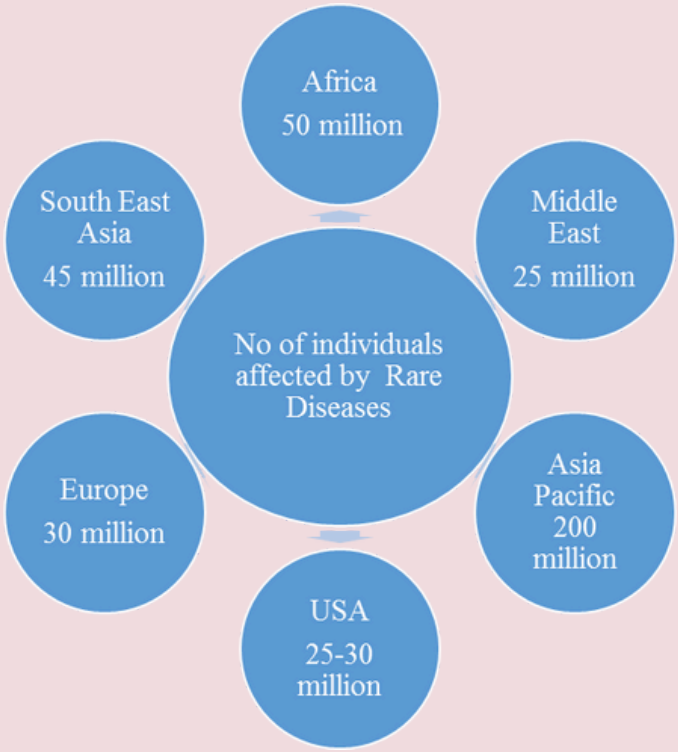

Figure 1. Number of individuals affected by rare diseases

3. Causes

3.1 Genetic mutations

Many rare and orphan diseases have a genetic basis, meaning they are result of mutations in the sequence of DNA. These mutations may be inherited from one or both parents (autosomal recessive, autosomal dominant) or occur spontaneously during embryonic development. Examples include Huntington's disease, cystic fibrosis, and Duchenne muscular dystrophy (12).

3.2 Environmental factors

Some rare diseases are influenced by environmental factors such as exposure to toxins, infectious agents, or certain drugs. Environmental triggers may interact with genetic predispositions to cause or exacerbate disease. For example, certain forms of cancer, autoimmune diseases, and metabolic disorders may have environmental components (13).

3.3 Immune dysregulation

Disorders characterized by dysregulated immune responses can lead to rare and orphan diseases. This category includes autoimmune disorders, which occur when the immune system targets the body's own tissues. Examples include systemic lupus erythematosus (SLE), multiple sclerosis (MS), and autoimmune hepatitis (14).

3.4 Metabolic abnormalities

Rare diseases may arise from abnormalities in metabolic pathways, leading to the accumulation or deficiency of certain substances within the body. Inborn metabolic errors, such as, maple syrup urine disease, phenylketonuria and Gaucher disease, can result in major health consequences (1

3.5 Structural abnormalities

Structural abnormalities in organs or tissues can give rise to rare diseases. These abnormalities may be present from birth (congenital) or develop later in life. Examples include congenital heart defects, craniofacial anomalies, and skeletal dysplasia (16).

3.6 Unknown causes

In some cases, the exact cause of a rare or orphan disease may be unknown or not well understood. Genetics and molecular biology advancement contributed to the identification of causative factors for many rare diseases, but there are still conditions for which the underlying mechanisms remain elusive (17).

4. Diagnostic challenges

People with orphan and rare diseases face numerous obstacles as a result of delayed or erroneous diagnosis, care, and treatments. Rapid diagnosis has become more important due to the exchange of genetic test results, new genetic sequencing techniques, and programs like Undiagnosed Disorders Network International (UDNI) and Undiagnosed Diseases Network (UDN) program that focus on undiagnosed disorders (18-21).

Genetic testing, including sequencing of whole genome and exome, has become a crucial diagnostic tool for identifying the genes linked to the onset of orphan diseases because it has been shown that defects in the mechanisms that repair single- and double-stranded DNA breaks are the cause of orphan diseases. Genetic counselling is critical in identifying and maintaining the good quality of life of people with rare disorders (22,23). DNA-powered applications are currently available to evaluate unprocessed DNA information from various sequences of genomes and genetic testing. In addition to figuring out how small molecules can be used to study genes that are responsible for the cure of rare or orphan disease, chemical genetics is becoming more and more popular these days. It can be used to uncover the molecular mechanism behind the neurological disorders development that are rarely reported, like ALS, DMD, SMA, and FAP (24).

5. Conclusion

Rare and orphan diseases collectively present a significant challenge to global health systems, primarily owing to their low prevalence and the lack of comprehensive treatment options. This article has explored the multifaceted impact of these diseases, highlighting the burden they place on affected individuals, healthcare systems, and societies worldwide. Despite the challenges, our analysis reveals progressive strides in specialized care and policy development aimed at addressing the needs of patients suffering from these conditions. To facilitate ongoing improvement, international collaboration must extend research, share expertise, and harmonize efforts in diagnostic processes, treatment protocols, and patient support mechanisms. Looking to the future, increased investment in medical research and policy innovation holds the key to unlocking better health outcomes for those affected by rare and orphan diseases. It is only through persistent effort and dedication to understanding and combating these conditions that we can hope to alleviate their impact and foster a more inclusive and responsive global health environment.

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Rare Diseases in India

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STIFFPERSONSYNDROME
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Answers are on page 187

Unveiling the enigmatic realm of rare diseases: A multidisciplinary odyssey towards elucidation, therapeutic innovation, and transformative hope




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Abstract

Despite their individual rarity, rare and orphan diseases collectively pose a significant burden on healthcare systems worldwide. This article delves into the complexities of these conditions, offering insights for patients, caregivers, and researchers. We explore resources from patient advocacy groups and government agencies, highlighting their role in supporting individuals and families. The importance of genetic testing in diagnosis and the potential of emerging therapies like gene editing are discussed. Additionally, the value of animal models in furthering our understanding and treatment factors for various diseases is addressed. By navigating this labyrinth, we can work towards a healthier option having rare and orphan diseases.

Keywords: Rare diseases, Orphan diseases, Diagnosis, Research, Treatment, Genetics, Gene therapy, Animal models

1. Introduction

The annals of medical science are replete with tales of discovery, perseverance, and triumph over the most formidable of adversaries - disease. However, amidst this narrative lies a fact which is shrouded in obscurity, a realm where the very notion of "rarity" poses profound challenges that reverberate across the global healthcare landscape. This realm is the domain of rare diseases, a constellation of conditions that, due to lower individual value, collectively impact millions of lives worldwide, leaving an indelible mark on patients, families, and communities alike. Unveiling the enigmatic nature of these disorders requires a multidisciplinary odyssey, one that integrates epidemiological insights, cutting-edge molecular research, and a steadfast commitment to therapeutic innovation and transformative hope.

2. Defining the boundaries of rarity through an epidemiological lens

The delineation of rarity in lie to diseases is a complex endeavor, steeped in epidemiological nuances and regulatory frameworks. In the United States, the Orphan Drug Act of 1983 established a prevalence threshold of less than 200000 patients to classify a condition as a rare disease.

Conversely, the European Union's Orphan Medicinal Products Regulation defines rarity as a condition affecting fewer than 5 in 10,000 individuals, or approximately 1 in 2,000 people. However, these numerical thresholds merely scratch the surface of the challenge, as it is thought to be around 6,000 and 8,000 distinct rare diseases identified to date, each with its own unique clinical manifestations, genetic underpinnings, and epidemiological patterns.

The true magnitude of this challenge extends far beyond mere statistics, as rare diseases can impact individuals across all ages, genders, and ethnic backgrounds, often with devastating consequences. Moreover, the epidemiological landscape of these conditions is further complicated by the inherent heterogeneity within and across populations, influenced by factors such as genetic variability, environmental exposures, and access to healthcare resources.

3. The diagnostic odyssey: Navigating the labyrinth of phenotypic heterogeneity

For individuals afflicted by rare diseases, the journey towards an accurate diagnosis is often an arduous and protracted ordeal, a labyrinth of uncertainty compounded by the inherent phenotypic heterogeneity of these conditions. Patients frequently endure a diagnostic odyssey that can span years, sometimes even decades, as they navigate a complex network of healthcare professionals, undergoing a myriad of tests and investigations in pursuit of answers amidst a landscape of limited knowledge and expertise (1,2).

The challenges associated with diagnosing rare diseases are manifold. Firstly, the low prevalence of these conditions often results in a lack of familiarity and specialized knowledge among healthcare providers, leading to misdiagnoses or delays in appropriate referrals. Additionally, many rare diseases exhibit a wide spectrum of clinical manifestations, making it challenging to establish clear diagnostic criteria and differentiate them from more common disorders.

Furthermore, the phenotypic heterogeneity of rare diseases can be influenced by factors such as age of onset, disease progression, and the presence of comorbidities, further complicating the diagnostic process. The average time to receive a definitive diagnosis for a rare disease can range from five to seven years, and in some extreme cases, it can take up to three decades, underscoring the basic and necessarily of , education, and diagnostic capabilities within the healthcare community.

4. The genetic tapestry: Unravelling the molecular underpinnings of rarity

A significant proportion of rare diseases, approximately 80%, are rooted in the intricate tapestry of our genetic code, presenting a formidable challenge for researchers and clinicians alike. These genetic disorders, with their own unique molecular signature, can manifest in a multitude of ways, affecting various organ systems, metabolic pathways, and developmental processes.

From rare forms of cancer driven by specific genetic mutations to debilitating neurodegenerative conditions caused by aberrant protein folding or accumulation, the spectrum of rare genetic diseases is vast and multifaceted, often pushing the boundaries of our current understanding of human biology and disease mechanisms.

Unravelling the molecular underpinnings of these conditions requires a multidisciplinary approach that integrates cutting-edge technologies such as high-throughput genomic sequencing, bioinformatics, and functional genomics. By deciphering the intricate correlation between genes, gene expression patterns, and cellular pathways, researchers can shed light on the underlying mechanisms driving these rare diseases, paving the way for the development of targeted therapeutic interventions (3-5).

Moreover, the advent of precision medicine and personalized therapeutics has created a new space for addressing the unique molecular signatures of rare diseases. By harnessing the power of genomics, proteomics, and advanced computational techniques, researchers are unravelling the intricate mechanisms underlying these conditions, enabling the design of tailored treatment strategies that account for individual genetic variability and disease-specific molecular profiles.

5. The treatment landscape: overcoming barriers and embracing innovative therapeutics

Navigating the treatment landscape for rare diseases is akin to traversing a treacherous terrain, fraught with obstacles and uncertainties. Despite the remarkable advances in fields such as genomics, proteomics, and personalized medicine, a staggering 95% of rare diseases currently lack an approved treatment. This sobering reality leaves patients and their families grappling with limited options and a relentless pursuit of relief, often turning to off-label use of existing therapies or experimental approaches as their only recourse.

However, the tide is shifting, as innovative therapeutic modalities are emerging from the convergence of scientific breakthroughs and a renewed commitment to addressing the unmet medical needs of those affected by rare diseases. Gene therapy, once a mere concept, has now become a clinical reality, offering hope for the treatment of genetic disorders by introducing functional copies of defective genes into the body's cells.

Enzyme replacement therapies, which provide missing or deficient enzymes to alleviate the manifestations of metabolic disorders, have also emerged as a promising therapeutic approach. These biologic agents are designed to supplement or replace the deficient enzymes, thereby restoring metabolic homeostasis and mitigating disease progression.

Furthermore, the advent of targeted small molecule inhibitors has opened new frontiers in the treatment of rare diseases. By selectively targeting specific molecular pathways or protein interactions implicated in disease pathogenesis, these compounds hold potential benefits (6,7).

6. Conclusion: Charting the path forward through multipronged strategies

The realm of rare diseases presents a formidable challenge that demands a multifaceted and coordinated response from various stakeholders, including researchers, clinicians, pharmaceutical companies, policymakers, and patient advocacy groups. As we chart the path forward, several key priorities emerge as critical to driving meaningful progress and improving outcomes for patients with rare disorders.

Firstly, establishing robust, global collaborative networks and centralized data repositories is paramount. These initiatives would facilitate the aggregation and analysis of epidemiological data, genomic information, and clinical outcomes, enabling researchers to identify patterns, elucidate disease mechanisms, and inform the design of targeted therapeutic interventions. Such comprehensive repositories would also aid in the acceleration of clinical trials and the development of precision medicine approaches tailored to the unique molecular signatures of rare diseases.

Secondly, sustainable funding mechanisms and innovative financing models are crucial to support the resource-intensive endeavours of rare disease research and development. Public-private partnerships, venture philanthropy, and outcome-based payment schemes could provide viable avenues for securing long-term investments in this field. Additionally, exploring novel incentive structures, such as transferable exclusivity vouchers or priority review pathways, may further incentivize pharmaceutical companies to engage in orphan drug development (8).

Thirdly, capacity building and knowledge dissemination within the healthcare sector are essential to address the diagnostic challenges associated with rare diseases. Implementing comprehensive training programs, developing clinical decision support tools, and fostering interdisciplinary collaborations among medical specialties can enhance awareness, improve diagnostic acumen, and streamline the patient journey towards timely and accurate diagnosis.

Fourthly, regulatory harmonization and policy reforms are imperative to ensure equitable access to approved treatments and supportive care services across diverse geographic regions and socioeconomic strata. Aligning regulatory frameworks, streamlining approval processes, and implementing reimbursement policies that prioritize rare disease therapies can help bridge existing disparities and ensure that no patient is left behind, regardless of their location or financial circumstances.

Lastly, and perhaps most crucially, actively engaging and empowering patients and their families throughout the research, development, and healthcare delivery processes is paramount. By incorporating patient perspectives, experiences, and priorities, we can ensure that rare disease research and clinical care are truly patient-centric, addressing the unique needs and challenges faced by those affected by these conditions (9,10).

The path towards transformative progress in the realm of rare diseases is undoubtedly arduous, but the rewards are immeasurable – the alleviation of suffering, the restoration of hope, and the preservation of human dignity. Through a concerted, multidisciplinary effort that harnesses the power of scientific innovation, policy reform, and patient advocacy, we can collectively navigate this uncharted territory, illuminating the way for those affected by rare diseases and ensuring that no one is left behind in the pursuit of better health and a higher quality of life.

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Deciphering the genetic and molecular landscape of orphan diseases: A comprehensive exploration

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Abstract

Orphan diseases, usually referred to as uncommon diseases, pose distinctive difficulties to the healthcare sector because of their low occurrence and frequently intricate causes. Although orphan illnesses are uncommon, they have a substantial aggregate impact, impacting millions of people globally. Recent advancements in genomic technology have significantly transformed our comprehension of the genetic and molecular foundations of many ailments. This comprehensive review delves into the complex molecular and genetic processes that underlie orphan illnesses, including issues such as the function of genomic diversity, molecular pathways, and treatment modalities. This review seeks to comprehensively explore the most recent research discoveries and future prospects in the subject, with the goal of enhancing our understanding of the genetic and molecular aspects of orphan diseases. By doing so, it hopes to provide the groundwork for advancements in diagnosis, therapy, and overall patient care.

1. Introduction

Orphan diseases refer to a diverse range of conditions that may only affect a tiny portion of the population individually, but when combined, they have a significant impact on millions of people globally. Orphan diseases, although uncommon, present substantial medical, scientific, and social difficulties. The limited comprehension of the fundamental processes, along with the absence of efficient therapies, frequently leads to delayed identification, insufficient medical attention, and unfavorable effects for affected persons. Recent developments in genomic technology, such as next-generation sequencing (NGS), have significantly improved our capacity to understand the genetic and molecular causes of rare disorders. This progress brings fresh optimism for both patients and healthcare professionals (1).

2. Epidemiology and classification of orphan diseases

Orphan illnesses are characterized by their low frequency, usually impacting less than 1 in 2,000 persons in the community. Nevertheless, as a whole, they include a broad spectrum of illnesses

that include several medical fields and clinical manifestations. Orphan illnesses are classified using several approaches, including different categorization systems that include factors such as the severity of the disease, the organs affected, and the genetic causes as given in table 1. The Orphanet classification, created by the Orphanet collaboration, offers a comprehensive system for classifying rare illnesses according to their clinical and molecular features. This system aids in research, diagnosis, and the development of treatments (2, 3).

Table 1. Classification of orphan diseases on the basis of prevalence, mode of inheritance and affected organ system

Criteria	Subcategories	Examples
Prevalence	Ultra-Rare Diseases (Prevalence < 1 in 1,000,000)	Nephronophthisis
	Rare Diseases (Prevalence < 1 in 2,000)	Cystic Fibrosis
	Common Rare Diseases (Prevalence 1 in 2,000 - 1 in 10,000)	Hereditary Hemochromatosis
	Less Common Rare Diseases (Prevalence 1 in 10,000 - 1 in 50,000)	Alkaptonuria
	Very Rare Diseases (Prevalence < 1 in 50,000)	Acromegaly
Mode of Inheritance	Autosomal Dominant	Marfan Syndrome
	Autosomal Recessive	Cystinosis
	X--Linked	Duchenne Muscular Dystrophy
	Y--Linked	Y--linked Hypogonadism
	Mitochondrial	Mitochondrial Encephalomyopathy
	Neurological Disorders	Huntington's Disease
	Cardiovascular Disorders	Hypertrophic Cardiomyopathy
	Metabolic Disorders	Phenylketonuria

Affected Organ System	Immunological Disorders	Comman Variable Immunodeficiency (CVID)
	Hematological Disorders	Hemophilia
	Respiratory Disorders	Cystic Fibrosis
	Gastrointestinal Disorders	Crohn's Disease
	Dermatological Disorders	Epidermolysis Bullosa
	Musculoskeletal Disorders	Osteogenesis Imperfecta
	Endocrine Disorders	Congenital Adrenal Hyperplasia (CAH)
	Renal Disorders	Polycystic Kidney Disease (PKD)
	Ophthalmological Disorders	Retinitis Pigmentosa
	Otolaryngological Disorders	Usher Syndrome
	Reeproductive Disorders	Turner Syndrome
Rare Cancers	Oncological Disorders	Neuroblastoma
Rare Genetic Syndromes	Syndromic Disorders	Down Syndrome

3. Genetic landscape of orphan diseases

Orphan diseases exhibit a diverse spectrum of mutations in their genetic makeup, including both single nucleotide abnormalities and massive genomic rearrangements. These mutations can happen in coding areas, regulatory elements, or non-coding sections of the genome, resulting in various clinical manifestations (4). Furthermore, orphan illnesses have diverse inheritance patterns, including autosomal dominant, autosomal recessive, X-linked, and sporadic types (5). Genome-wide association studies (GWAS), whole-exome sequencing (WES), and whole-genome sequencing (WGS) have played a crucial role in discovering genetic variations that cause diseases and understanding how these diseases develop (6). Orphan illnesses encompass a range of genetic abnormalities, each characterized by its own genetic profile. Certain illnesses arise from mutations in a solitary gene, whereas others may entail intricate interplay among numerous genes and environmental variables (7). Moreover, the presence of diverse genetic variations in rare diseases adds to the range of clinical characteristics, which in turn makes the process of diagnosing and treating these diseases more difficult.

4. Molecular mechanisms underlying orphan diseases

The molecular mechanisms responsible for orphan diseases are varied and involve a broad spectrum of biological processes, including as protein misfolding, aberrant gene expression, dysregulated signaling pathways, and altered cellular homeostasis (8). Orphan illnesses often arise from malfunctions in crucial cellular processes, such as protein folding, degradation, and trafficking. These malfunctions can cause cellular dysfunction and harm to tissues. Through molecular research, it has been discovered that seemingly unrelated orphan illnesses really have similar pathways and molecular networks. This finding emphasizes the possibility of using focused therapeutic interventions and drug repurposing methods to treat these diseases (9).

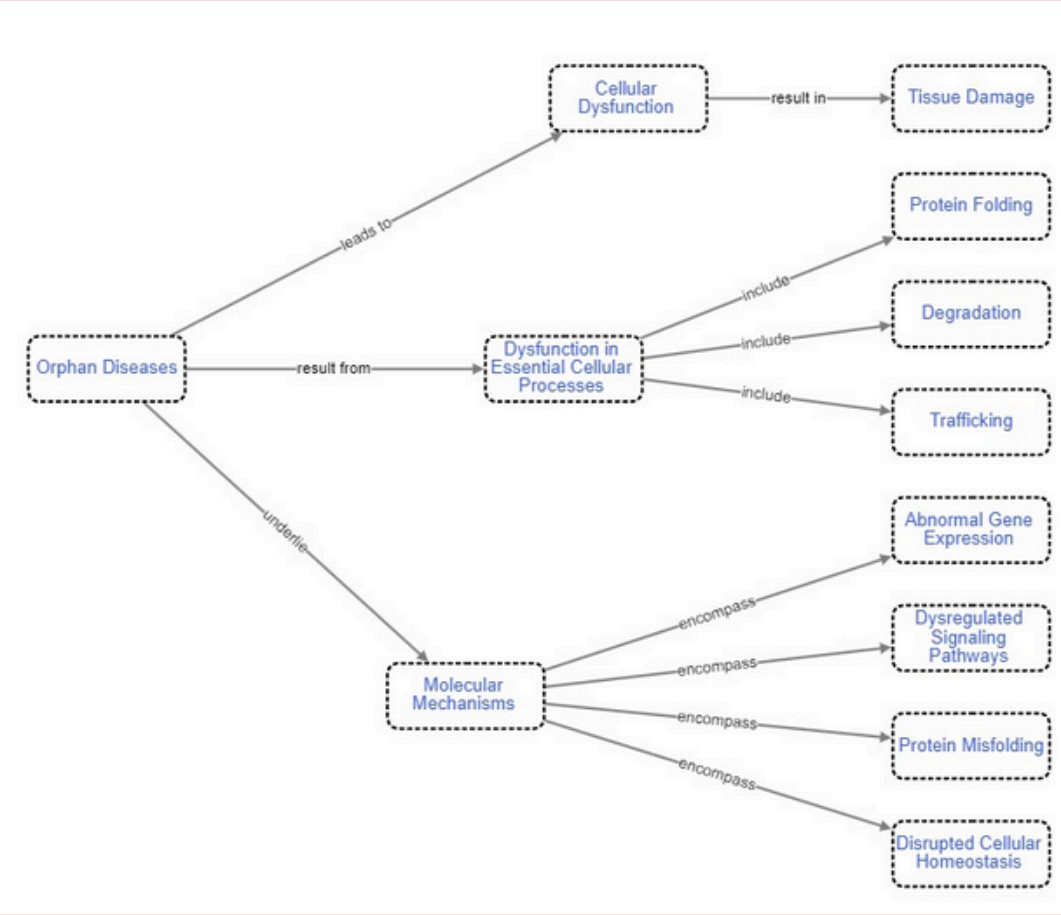

Figure 1. Molecular mechanism and cause of orphan diseases

5. Diagnostic challenges and advances in rare disease identification

Diagnosing orphan diseases poses distinct issues due to their infrequency, variety in physical characteristics, and frequent overlap in clinical symptoms with more prevalent ailments. Patients with rare diseases may have a long and stressful journey to get a diagnosis, which involves seeing several healthcare specialists, undergoing rigorous testing, and facing delays in receiving a conclusive diagnosis. Advancements in genomic and molecular diagnostics have greatly transformed the diagnostic procedure for several rare diseases, allowing for rapid and precise detection of genetic variations that cause the disorders. The utilization of next-generation sequencing (NGS) technology, in conjunction with bioinformatics analysis and functional validation studies, has greatly improved our capacity to detect rare diseases that lack a known cause. This advancement has made it easier to intervene early and develop tailored therapy approaches (10).

6. Therapeutic Approaches and Drug Development for Orphan Diseases

Developing effective remedies for rare diseases presents notable obstacles, such as a limited number of patients, inadequate understanding of disease causes, and elevated costs associated with development. Recent advancements in the fields of drug development, precision medicine, and gene therapy provide new possibilities for treating orphan illnesses. Enzyme replacement therapy (ERT) and small molecule inhibitors are specific treatments that have greatly transformed the management of some uncommon ailments. These medicines effectively alleviate symptoms and enhance the overall well-being of affected persons. Gene therapy methods, such as gene editing and gene silencing technologies, show potential for rectifying fundamental genetic abnormalities in rare illnesses, providing the possibility of curative therapies.

7. Patient advocacy and community engagement in rare disease

Campaigning organizations and communities dedicated to rare illnesses are essential in promoting research, increasing awareness, and fighting for better healthcare access for persons affected by orphan diseases. These organizations offer assistance, materials, and advocacy for individuals and families impacted by uncommon conditions, promoting scientific investigations and fostering cooperation among involved parties. Patient registries, internet forums, and social media platforms are useful resources for linking persons with rare illnesses, promoting peer support networks, and exchanging information regarding clinical trials and treatment choices. Rare illness advocates play a crucial role in promoting orphan disease research and the creation of patient-centered care models by amplifying patient voices and campaigning for legislative reforms. A significant obstacle in the field of orphan disease research is the scarcity of resources and infrastructure dedicated to the study of uncommon disorders. Orphan diseases, in contrast to more prevalent illnesses, can suffer from a lack of specific research funding and clinical experience, which poses challenges in conducting thorough investigations. Moreover, the limited number of patients and their scattered geographical locations, which are typical of rare diseases, provide difficulties in enlisting volunteers for clinical trials and genetic research (11).

8. Future directions

Anticipating the future, the field of orphan illness research is highly promising. The rapid progress in genomic technologies, including single-cell sequencing, CRISPR-Cas9 gene editing, and multi-omics integration, has the capacity to reveal new disease processes and targets for therapy (12). In addition, efforts such as the International Rare Diseases Research Consortium (IRDiRC) and the Orphan Drug Act have the goal of expediting the progress of orphan medications and enhancing patient outcomes (13). Through the utilization of multidisciplinary teamwork and advanced technology, we may further explore the complex genetic nature of rare illnesses and establish personalized precision medicine strategies for specific patients.

9. Conclusion

In conclusion, the genetics and molecular basis of orphan diseases represent a complex and multifaceted area of research. Through ongoing efforts to elucidate disease mechanisms, identify therapeutic targets, and improve diagnostic capabilities, we can address the unmet needs of individuals affected by these rare conditions. By fostering collaboration, advocating for increased research funding, and embracing technological innovations, we can strive towards a future where every patient, regardless of the rarity of their disease, has access to personalized and effective treatments.

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Empowering patients with rare diseases: Strategies for overcoming challenges and promoting self-advocacy

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Abstract
Patients with rare diseases often face significant challenges, including delayed diagnosis, limited treatment options and inadequate support systems. Empowering these patients involves a multifaceted approach that enhances their advocacy, education and access to care. We can significantly improve the quality of life for rare disease patients by collaboration among stakeholders, patients, healthcare providers, advocacy groups and focusing on the key areas offering them hope and the potential for better health outcomes.

1. Introduction

The medical conditions that affect a relatively small number of people compared to other, more common illnesses are termed as Orphan and rare diseases. These Orphan diseases generally receives less attention may be due to limited market potential for developing treatments. Many patient advocacy groups work globally to support research, raise awareness and improve the lives of patients with rare diseases. Patient advocacy plays a vital role in the Orphan and rare disease community and improving outcomes for patients and their families. Raising awareness in rare disease patient empowerment is a multifaceted effort aimed at increasing knowledge and understanding of rare disease among general public, healthcare providers and researchers.

2. Education and outreach programs

Various educational programs and outreach initiatives were develop and implement by Patient advocacy organizations to raise awareness about specific rare diseases. These programs may include webinars, workshops, seminars and providing educational materials targeting patients, their families and healthcare providers. Patient empowering starts by providing them useful information about their condition, including its causes, symptoms, prognosis, treatments option and various lifestyle adjustments or management strategies. Along with this, various media outlets that highlights the challenges and needs associated with rare diseases are also comprehensively informed. Education and outreach programs focused on rare diseases serve an important role in bridging gaps in knowledge, support and resources. It helps in empowering patients and families better equipped to manage health conditions. This knowledge enables patients to make informed decisions about their care and advocate for themselves effectively (1).

3. Public awareness campaigns

Advocacy groups may set up public awareness campaigns to increase visibility, understanding and support for rare diseases. It helps in increasing public awareness about existence and challenges of rare diseases or for the conditions that are often overlooked. It generates interest and funding resources for the development related to treatment and potential cures. Awareness campaigns require careful planning, robust engagement strategies as because rare diseases affects small number of people that makes it challenging to capture public interest. These campaigns often utilize traditional and digital media channels, social media platforms, and community events to reach a wide audience and share information about rare diseases, their symptoms, diagnosis and available resources (2).

4. Advocacy events and awareness days

One of the advocacy event like Rare Disease Day celebrated on 28th February of every year to provide opportunities for individuals and organizations to come together to raise awareness, share information and advocate for policy change. Advocacy events are designed to engage with policy makers, healthcare providers and broader public to drive changes that benefit the rare disease community. The purpose of this event is to educate the stakeholders about importance of supporting research funding, healthcare reforms and policies. These advocacy events often include rallies, legislative conferences, testimony from patients and experts, panel discussions on specific needs, fundraisers and social media campaigns to amplify the voices of the rare disease community (3).

Capitol Hill days that directly engages elected officials to discuss rare disease community needs, are kind of advocacy events. In this event, group of individuals gather in the capital city, often in the United States, to meet with lawmakers and advocate for specific policies or causes. It plays an important role in pushing for changes that significantly impact healthcare policy and research funding and also in improvement of drug development incentives. Awareness days are vital for educating the public and rallying support around the globe. Each year, on awareness day a thematic campaign is organized that highlights a particular aspect of rare diseases .Such events and awareness days are awareness tools in fight to bring attention and resources to rare disease community (4).

5. Storytelling and patient narratives

Storytelling and patient narratives are one of the powerful tools for raising awareness, fostering empathy and driving change within rare disease community. These narratives provide a human face to the statistics and medical jargon, helping to connect with audiences on a personal level. These are the personal stories and experiences of individuals affected by rare diseases. Patient advocacy organizations highlight patient narratives through websites, social media and written publications to humanize the impact of rare diseases and inspire action (5).

6. Collaboration and partnerships

Collaboration and partnerships are essential in addressing the complex challenges associated with rare diseases. No single entity can effectively tackle such issues alone having limited resources, expertise and patient population. Different groups or collaborations like research includes pharmaceutical companies that can accelerate drug discovery and clinical trials, academic institutions that conduct basic research, government agencies i.e National Institute of Health (NIH) or European medicines agency that provides funding and regulatory support. Collaboration with biotech firms helps in developing diagnostic tests, biomarkers and personalized therapies for rare diseases and also patient-reported data or exchange of genomic data for research purpose by data sharing companies (6). Partnership leads to enhanced patient care, improving outcomes and quality of life. It strengthens advocacy by increasing influence in policy discussions and decision making process. Partnerships can accelerate research among academia, industries and government. Besides having enormous benefits, collaboration and partnership faces challenges like sustainability, effective communication among stakeholders, data protection, regulation ensurance as well as clear agreements regarding Intellectual Property Rights (7).

7. Legislative and self-advocacy

Advocacy groups advocate for legislative initiatives and policies that benefit individuals affected by rare diseases. This may include advocating for increases funding for research, incentives for orphan drug development, improved access to healthcare services and protections for patient's rights. Empowering patients involves encouraging them to advocate for their needs and rights within the healthcare system and society at large. Also increases access to treatments, participating in research initiatives, raising awareness about their condition and promoting policy changes that benefit the rare disease community (8).

Legislative advocacy and self- advocacy both are essential strategies for addressing the unique challenges faced by rare disease patients. Legislative advocacy helps in identifying priorities of research funding through various government agencies, push for regulatory reforms that streamline the orphan drug development process and incentives. Also plays an important role in building relationships with elected officials, advocacy groups, healthcare providers for amplify the collective voice of rare disease community. It provides policy education by briefing information, data and personal stories that highlight the importance of addressing rare diseases and participation in advisory panels before experts. Self- advocacy empowers individuals affected by rare diseases to assert their rights, access necessary resources and advocate for their own needs. It builds up knowledge and awareness in understanding rights as a patient, assessment of healthcare and privacy protection including option for treatment and creating a network of support and solidarity (9).

8 . Shared decision-making

Encouraging shared decision- making between patients and healthcare providers allows patients to actively participate in their treatment plans. By involving patients in discussions about treatment options, risks and benefits. Healthcare providers can ensure that care plans align with patient's preferences, values and goals. Providing patients with clear, unbiased information about their condition, treatment options, risks, benefits and uncertainties helps in patient autonomy. The key components behind shared decision- making are Information exchange about patient's condition, deliberation, improved communication. It also incorporates with many challenges and barriers i.e. time constraints, cultural and linguistic differences, health literacy and power imbalance (10).

9. Health literacy and communication building

Empowering patients involves promoting health literacy and communication skills to effectively navigate the complexities of the healthcare system, communicate with healthcare providers, ask questions and express concerns. This helps patients in managing their health. Communication building in the context of rare diseases involves creating networks of support, advocacy and collaboration among patients, caregivers, healthcare providers, researchers and stakeholders. Patient and family support by online forums and support group, peer mentoring programs, various campaigns and events or collaborative advocacy efforts builds up good communication. Research collaboration involves patients and caregivers in all stages of research process, from study design and recruitment to data analysis and dissemination of results. Adopts Community- based Participatory research (CBPR) approaches that prioritize rare disease community (11).

10. Self-management skills

Patient empowerment involves equipping individuals with the skills and resources they need to actively manage their condition on a day- to- day basis. This may include teaching patients techniques for symptom management, monitoring their health status, adhering to treatment regimens and recognizing signs of complications. Self-management skills include health literacy by understanding the condition and familiarize to medical terminologies. Symptom monitoring by

using symptom tracking tools such as diaries, apps or wearable devices, to document symptoms, triggers and patterns over time. Medication management by adhering to prescribed medications, including dosage, schedules and potential side effects. Healthy lifestyle practices by adopting a balanced diet incorporate regular physical exercise and healthy sleep habits. Stress management by relaxation techniques, mindfulness and stress reduction activities. By empowering patients with the knowledge, skills and resources they need to take an active role in their own care, we can improve quality of life and foster resilience in the face of rare diseases (12).

11. Conclusion

Empowering patients with rare diseases is a multifaceted endeavour that requires collaboration among patients, caregivers, healthcare providers, researchers and policymakers. By empowering patients to become active participants in their own care, we can foster resilience, promote well-being and create a more inclusive and supportive healthcare system for individuals affected by rare diseases.

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Rare and orphan diseases: Challenges and opportunities


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Abstract
Rare and orphan diseases, also known as rare disorders, encompass a diverse array of prerequisites which collectively impact a substantial number of people worldwide. Despite their low individual prevalence, these diseases pose multifaceted challenges for patients, health stakeholders, and pharmaceutical companies. This comprehensive review article delves into the intricate landscape of rare and orphan diseases, exploring their definition, epidemiology, diagnostic complexities, treatment options, and the ongoing efforts to change the unique hurdles associated with these conditions. By shedding light on this often-overlooked area of healthcare, we aim to bring the issue to light and encourage widespread understanding, and ultimately pave the way for improved outcomes and quality of life for those affected by these rare disorders.

Keywords: Rare diseases, Orphan diseases, Diagnosis, Precision medicine, Orphan drugs

1. Introduction
Rare and orphan diseases are a heterogeneous group of conditions characterized by their low prevalence, typically affecting fewer than 200,000 individuals in the United States or fewer than 1 in 2,000 individuals in the European Union (EU). These disorders can be inherited or acquired, affecting individuals across all ages, genders, and ethnic backgrounds. The term "orphan" is derived from the historical lack of commercial interest from pharmaceutical companies in developing treatments for these conditions due to the small patient population and the perceived low return on investment. However, recent advancements and policy changes have catalyzed a shift in this landscape, with increasing recognition of the urgent need to address the unmet medical needs of those affected by rare diseases.

2. Epidemiology and classification
Depending on different sources, the number ranges from 6,000 and 8,000 distinct rare diseases identified worldwide, collectively affecting millions of people globally. Accurately measuring the prevalence of these conditions is often a hurdle to determine due to the lack of comprehensive, centralized registries and the inherent challenges associated with diagnosis. Rare diseases can be classified based on their underlying etiology, affected organ systems, or specific characteristics, encompassing a wide range of disorders, including genetic or metabolic disorders, rare cancers, autoimmune diseases, and rare infectious diseases (1-3).

3. Diagnosis and challenges
The journey to an accurate diagnosis for individuals with rare diseases is often arduous and fraught with numerous obstacles. Many patients experience a protracted diagnostic odyssey,

enduring multiple misdiagnoses, referrals, and extensive testing before finally receiving an accurate diagnosis. This diagnostic delay may have significant consequences for disease management, treatment outcomes, and the overall well-being of patients and their families. Furthermore, the lack of awareness and specialized knowledge among healthcare professionals regarding these rare conditions can exacerbate the diagnostic challenges, leading to further delays and misdiagnoses.

Table 1. This table provides relevant statistics and information on the epidemiology, diagnosis, treatment, regulatory frameworks, patient advocacy, and funding aspects related to rare and orphan diseases.

Parameter	Statistics/Information
Estimated number of rare diseases worldwide	6,000 - 8,000
Collective population affected	Millions of individuals
Prevalence threshold for diseases in the US	Affecting fewer than 200,000 individuals
Prevalence threshold for diseases in the EU	Affecting fewer than 1 in 2,000 individuals
Percentage genetic etiology	Approximately 80%
Percentage affecting children	Estimated 50%
Average time to receive an accurate diagnosis	5--7 years (in some cases, up to 30 years
Number of approved drugs in the US (as of 2022)	Over 600
Number of approved drugs in the EU (as of 2022)	Around 200
Estimated cost of developing	$500 million - $1 billion
Average annual cost	$150,000 - $500,000
Percentage with no approved treatment	Approximately 95%
Percentage with no approved treatment	Over 7,000
Estimated annual funding research in the US	$3.7 billion (NIH, 2022)
Estimated annual funding in the EU	€1.5 billion (Horizon Europe, 2021-2027)

4. Treatment and therapeutic development

Treatment availability for rare diseases are frequently limited or non-existent, leaving patients and their families grappling with significant unmet medical needs. For some conditions, supportive care and symptom management may be the only available approach, while later may have a upper hand from off-label use of existing therapies. However, in recent years, advances in fields such as genomics, molecular biology, and personalized medicine have paved the way for the development of targeted therapies tailored specifically for rare diseases (4). These innovative approaches include gene therapy, enzyme replacement therapy, and small molecule drugs designed to target the underlying molecular mechanisms of these conditions. Despite these promising advancements, the substantial financial burden of research and development combined with the small patient population, can make it challenging for pharmaceutical companies to justify the substantial investment required to bring these therapies to market (5).

5. Regulatory frameworks and incentives

Recognizing the unique challenges associated with rare and orphan diseases, various regulatory frameworks and incentives have been established to encourage and facilitate research and development in this field. In the United States, the Orphan Drug Act of 1983 was a pioneering legislative effort that provided financial incentives, such as tax credits, market exclusivity, and fee waivers, for pharmaceutical companies engaged in developing treatments for rare diseases. Similarly, the European Union established the Orphan Medicinal Products Regulation, offering comparable incentives to promote research and development efforts focused on addressing the unmet medical needs of patients with rare disorders.

6. Patient advocacy and support

Patient advocacy organizations play a pivotal role in the rare disease ecosystem, serving as a powerful voice for those affected by these conditions. These organizations tirelessly raise awareness, provide invaluable support, and advocate for the rights and needs of individuals living with rare diseases and their families. They often serve as a vital bridge, facilitating collaboration and communication among patients, healthcare providers, researchers, and policymakers, driving progress in research, diagnosis, and treatment. Additionally, patient advocacy groups offer a range of educational resources, support groups, and practical assistance in navigating the complexities of the healthcare system, ensuring that no patient or family member faces these challenges alone (6).

7. Challenges and future directions

Despite the significant strides made in recent years, numerous challenges persist in the field of rare and orphan diseases, impeding progress and limiting access to effective treatments and supportive care. One of the most pressing challenges is the lack of comprehensive, global registries and data repositories, which hinders our ability to accurately track and study these conditions. Additionally, limited funding for research and the urgency of fostering collaboration among key players pose significant barriers to advancing our understanding and developing novel therapies (7,8).

Moreover, even when approved treatments become available, access can be limited, particularly in resource-constrained settings or regions with inadequate healthcare infrastructure. Addressing these multifaceted challenges requires a concerted and collective action in healthcare. To drive progress and improve outcomes for those affected by rare diseases, several initiatives and strategies have been proposed:

7.1 Establishing robust international collaborations and data-sharing platforms to facilitate research efforts, enhance our understanding of these rare conditions, and accelerate the development of effective treatments.

7.2 Promoting public-private partnerships and exploring innovative funding models to support and incentivize research and development initiatives targeting rare diseases.

7.3 Enhancing awareness and education among healthcare professionals to improve diagnosis, management, and access to available treatments and supportive care services.

7.4 Advocating for policies and healthcare reforms that prioritize equitable access to approved treatments, supportive care, and comprehensive services for patients with rare diseases, regardless of their geographic location or socioeconomic status.

7.5 Encouraging active patient involvement and engagement throughout the research and development process, ensuring that patient perspectives, needs, and priorities are at the forefront of these efforts (9,10).

8. Conclusion

The landscape of such diseases is complex, multifaceted, and presents a different area that require a coordinated and multidisciplinary approach. Despite the significant strides made in recent years, driven by scientific advancements, policy reforms, and the tireless efforts of patient advocacy groups, the journey towards achieving comprehensive and equitable care for those affected by these conditions is far from over.

As we look towards the future, several key priorities emerge as critical to driving meaningful progress and maintaining consequences for patients with rare diseases:

8.1 Establishing robust, global collaborative networks and data-sharing platforms: By fostering international collaborations and centralizing data repositories, we can accelerate research efforts, enhance our motive of the mechanisms and natural history of these conditions, and expedite the development of effective diagnostic tools and targeted therapies.

8.2 Sustainable funding and innovative financing models: Addressing the significant financial barriers that hinder research and development initiatives requires a concerted effort to secure sustainable funding sources and explore innovative financing models. Public-private partnerships, venture philanthropy, and outcome-based payment models could provide high knowledge for supporting rare disease research and ensuring access to approved treatments.

8.3 Strengthening healthcare infrastructure and capacity building: In many regions, limited healthcare resources, inadequate infrastructure, and a lack of specialized expertise pose significant barriers to timely diagnosis, proper management, and access to available ailments of such diseases. Investing in capacity building, education, and training for professionals in healthcare sector, as well as strengthening healthcare systems, is crucial to ensuring equitable access to comprehensive care.

8.4 Patient-centered approaches and engagement: Placing patients at the center of rare disease research, policy development, and healthcare delivery is essential for ensuring that their needs, priorities, and perspectives are adequately addressed. Encouraging active patient engagement throughout the research and development process, as well as in the design and implementation of supportive care services, can lead to more meaningful and impactful outcomes.

8.5 Regulatory harmonization and policy reforms: While regulatory frameworks and incentives have been instrumental in driving rare disease research, there is a need for greater harmonization and coordination among different regions and countries. Streamlining regulatory processes, aligning incentives, and implementing policies that prioritize access to approved treatments and supportive care services can help overcome geographic disparities and ensure that no patient is left behind.

Addressing the multifaceted challenges associated with rare and orphan diseases requires a concerted, global effort that transcends borders and disciplines. By fostering collaboration among patients, researchers, pharmaceutical companies, policymakers, and other stakeholders, we can collectively work towards a future where no disease remains truly orphaned, and where those affected by these conditions have access to timely diagnosis, effective treatments, and comprehensive supportive care services, ultimately improving their quality of life and reducing the immense burden imposed by these rare disorders.

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Invisible illnesses: Shining a light on the psychosocial impact of rare diseases

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Abstract
Rare diseases (RDs) impact a small proportion of the population yet can be very debilitating and dangerous. People with RDs suffer unique and substantial obstacles as a result of the infrequent nature of their medical diseases, such as a lengthy diagnostic process, insufficient clinical care, and restricted access to appropriate medications. Historically, patient groups have been the primary drivers behind increasing awareness about these diseases and fighting for government supportive legislation. The burden of RD on patients, caregivers and families, healthcare systems, and society as a whole deserves more exposure and appreciation. Taken together, scientific, social, ethical, and political responsibilities call for more RD inclusion and integration in research and policies, thereby advancing the goal of the UN Resolution to "leave no one behind."

1. Introduction
Invisible illnesses, particularly rare diseases (RDs), pose distinct challenges not just because of their clinical symptoms, but also because of the psychological effect that they have. These illnesses are frequently not well-known in popular culture, which makes it challenging for those who are impacted by them to get sympathy and assistance from the community. The sense of loneliness is a major component of the psychosocial effects of rare illnesses. People with these disorders may find it difficult to get empathy and support from friends, family, and even medical experts because these conditions are frequently poorly understood by others. The already difficult experience of managing a rare illness can be made worse by this sense of isolation, which can result in emotions of loneliness, sadness, and anxiety (1), as mentioned figure 1.

Physiological effects	Social implications	Functional impact
• Low mood • Frustration • Anxiety • Fear • Uncertainty for future • Irritability • Difficulty in making decisions • Restlessness • Muscle tension • Changes in eating habits	• Difficulties in explaining the symptoms to close friends and family • Difficulty in justifying to not present at workplace and school • Isolation due to difficulty of finding other people with the same diagnosis • Lack of psychological care • Difficulty in planning everyday life • Difficulty accessing resources or benefits • Financial difficulties due to the disease	• Loss of independence due to the disease • Loss of abilities due to the disease • Loss of work or academic opportunities due to the disease

Figure 1. Psychological impact on people affected by RDs

Children, adolescents, and their families are rarely affected by RDs, but their impact is vast. US National Institutes of Health characterises such illnesses as occurring once in 200,000 or less, criteria differ worldwide (2). The US definition is tied to the 1983 Orphan Drug Act, which was enacted to incentivize the pharmaceutical sector to study and develop novel medicines for rare diseases (3). In the United States, these ailments are known as "orphan diseases" because the law was known as the Orphan Drug Act (4). More common orphan and RDs include cystic fibrosis, Lou Gehrig's disease, and Tourette's syndrome; less common ones include Duncan's syndrome, Madelung's illness, and acromegaly/gigantism. Often, the prevalence of RDs is an estimate that is subject to change over time. Due to the complexity and common misinterpretation of these conditions, many people find it more challenging to be properly diagnosed or receive the right therapies. Effective therapies ought to be put into place as soon as the ailment has been discovered. Effective targeted treatments that can change the course of the disease and greatly enhance patient and family outcomes and quality of life are only available for 5% of RDs (5). Regretfully, orphan drugs are not only rare but also quite expensive, and their accessibility varies greatly between and within nations (6). The availability of medicines for children is quite restricted: even the pharmaceuticals that are currently on the market are often not designed with children in mind, and the necessary clinical trials to assess their efficacy and safety in this demographic have not been carried out (7). For both common and uncommon disorders, the same strategy applies: we need to understand the underlying mechanisms of the illness, pinpoint the biological targets that can be targeted with medication, and develop new therapeutics. However, the very first step towards the development of medicines—elucidation of pathological mechanisms—has been taken in only about 1000 of all (up to 8000) rare diseases (8). Additionally, the necessary research infrastructures—such as biobanks for most illnesses and patient registries for studies on the natural course of diseases or cohort collections for clinical investigations—are not available. As a result, specific treatments for the majority of the other 7000 RDs are not even on the horizon, and certain RDs appear to be "undruggable" (such as chromosomal diseases) (9).

2. Challenges with RDs

In India, not only is the general populace unaware about RDs, but so are healthcare providers and policymakers. Compared to developed countries such as the US, India is about 40 years behind in realising the need of combating RDs. In developing countries, much of the effort to combat such diseases is concentrated on obtaining orphan medications. There has been little focus on building registries, genetic screening, access to therapy, (10) health insurance coverage, and public perception of these disorders.

India must adopt a decentralised approach to RDs, using epidemiological data to inform policy and legislation. Such policies should allow for the capture and sharing of electronic health data while also protecting individuals' privacy. Evidence from advanced economies shows that patients struggling with RDs are nearly 90% more likely to share their data for further research than others. India should also aim to create, protect, and promote such recording practices (11). Policies should accelerate scientific innovation and advanced clinical research while also allowing key stakeholders such as patients, doctors and carers, and the pharmaceutical sector to connect more easily.

The National Digital Health Mission (NDHM) can aid in the diagnosis of RDs. Various cutting-edge diagnostics were created during the COVID-19 pandemic and can be utilised for RDs. However, Indian specialists feel that scaling these capabilities to the local level will be challenging, even though the country's bio-community already uses them extensively. Traditional views must alter for therapies to evolve and embrace modern technological advancements in a variety of ways (12). Most RDs necessitate ongoing therapy and assistance for the patient to maintain a

reasonable quality of life. Caregiving depletes families physically, emotionally, and financially. As a result, palliative care, rehabilitation, and psychotherapy services must be included as part of the RD management process. Significant resources are necessary, as well as strong government support. It can be challenging for countries like India to shift resources from more common general diseases to RDs. However, reduced occurrence should not be seen as less significant. Implementing the NPRD is merely one step towards resolving the issues of RD management (12).

3. Future directions

RD patient organisations can promote policy adoption and help coordinate treatment (13). Governments ought to use in-depth conversations and patient advocate focus groups to increase public awareness of the needs of RD populations. On one side, patient groups for RDs are essential in promoting patient rights and opportunities for research. On the other side, patient organisations provide the basis for patients' and their families' psychological assistance. Leading the effort were RDs International, EURORDIS (rare disease-Europe), and the Committee on NGOs for RDs, which resulted in the recently passed historic UN Resolution on RDs. It advocates for greater integration and gives the RD population priority on the UN agenda, which represents a dramatic change in the global policy landscape (14). This international campaign brings attention to the needs of the RD community, which makes it possible to develop critical plans and strategies for providing affordable and easily accessible care. RD patient associations can empower patients as well as care takers by being the voice of the RD population, raising awareness and educating the public at the same time. By shedding light on the psychosocial burden of rare diseases and collaborating to raise awareness and support, we can meet the needs of individuals and families affected by these often-ignored conditions.

The last ten years have seen tremendous advancements in RD research, which have fundamentally altered the worldwide policy environment. Among these advancements are the three 10-year goals set forth by International Rare Disease Consortium (IRDiRC) and the UN Resolution that was approved in December 2021 highlighting the need of integrating the RD population in the UN 2030 agenda. Prior research has emphasised about the significance of an early diagnosis as well as the substantial effects of RDs on patients' socioeconomic burden and quality of life (15-16). It is critical to recognise that a lack of medical understanding, a lack of social support system, and a lack of public awareness of RDs are the primary causes of the physical, social, and economic effects of RDs. As RD becomes a worldwide public health concern, RD policies and initiatives in the areas of healthcare, social care, insurance, education, and many more are required to provide a more fair and inclusive community for the RD population. Future research and analysis on RD will probably advance our understanding of all diseases. Here, we suggest that RDs adopt patient-centered, multidisciplinary action plans in the future, with an emphasis on the execution of educational and training initiatives, the abolition of stigmatisation and discrimination, and the formation of an international coalition among multidisciplinary stakeholders (14).

4. Conclusion

In conclusion, RDs have profound negative impacts on patients, their families, and societies, and RD patients often face many challenges to have their needs met. RDs are only recently and progressively becoming a policy priority for the UN and WHO, extending an invitation to increase health policies and initiatives at the regional and country levels. The creation of mobile applications (apps), wearable technology, and remote sensors will all help with the ongoing patient monitoring process to ensure the efficacy and safety of both licenced and experimental drugs. Access to knowledgeable physicians who possess a deeper comprehension of specific uncommon diseases could be facilitated by telehealth and telemedicine (17). Taken together, scientific, social, ethical, and political responsibilities call for more RD inclusion and integration in research and policies, thereby advancing the goal of the UN Resolution to "leave no one behind."

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2nd Leadership APTI Women's Residential Conclave in Udaipur, Rajasthan: A Transformative Gathering in City of Lakes

2nd Leadership APTI Women's Residential Conclave in Udaipur, Rajasthan: A Transformative Gathering in City of Lakes

The APTI Women Forum's 2nd Leadership Residential Conclave was held in the city of lakes, Udaipur, Rajasthan, from 29th to 30th March, 2024. It proved to be a noteworthy event which aimed at empowering and uniting women from pharmaceutical academia and enhancing leadership skills amongst the participants. Fifty selected delegates from different part of the country checked into the mesmerizing venue of Radisson Blu Resort & Spa, Udaipur on 28th March, 2024. The venue nestled amidst the Aravalli Hills adorned with serene lakes captivated the heart of all the attendees. The program was inaugurated on 29th March morning with invocation of blessings of Goddess Saraswati in melodious voice of Prof. Suneela Dhaneshwar followed by a welcome address by Prof. Vandana Patravale, National Convener, APTI Women's Forum who outlined the mission and vision of APTI Women's forum. She also highlighted the major objectives of the conclave and presented a comprehensive overview of the various activities carried out by APTI Women's Forum. The Guest of Honor Ms. Maharukh Rustomjee, Founder and Managing Partner, Amaterasu Lifesciences LLP, Mumbai in her address highlighted about gender equality, essential components of leadership and how women leaders can overcome the challenges through her life experiences. She emphasized on how women leaders bring positive changes that have constructive impact on society and in the country's economy. The distinguished Chief Guest Prof. (Dr.) Balvinder Shukla, Hon'ble Vice chancellor, Amity University, Noida, emphasized that women empowerment is a journey that begins at home itself. She through her life story shared the importance of man in making woman empowered. She also highlighted the importance of maintaining ecosystem at home so that woman can serve at her best as a leader at home and at workplace. She made attendees understand their self-worth in order to progress and shine despite of huge gender inequality at workplace.

Both the guests highlighted limitless capacity and capability of women, and how it is essential to place them at the forefront of the economic and social sectors to establish new dimensions of national development. They also spoke about the need for inclusive policies, institutional support, and cultural shifts to create conducive environments for women's advancement. The Guest's Personal anecdotes and real-life examples added depth and authenticity to the speeches, resonating with the audience on a profound level.

On this occasion, the APTI Women Forum's newsletter on the theme "Green and Sustainable Practices for Pharmaceutical Industry" was unveiled at the hands of Chief Guest Prof. (Dr.) Balvinder Shukla, Guest of Honor Ms. Maharukh Rustomjee, Resource Person Ms. Vijayalakshmi, Dr. Vandana Patravale, Dr. Indupal Kaur, Dr. Suneela Dhaneshwar, Dr. Kamla Pathak, and the program coordinators Dr. Pallavi Ahirrao, Dr. Rashmi Trivedi and Dr. Udichi Kataria

Dr. Milind Umekar, National President, APTI addressed the attendees through a video message and highlighted the ongoing drives of APTI all over nation for betterment of pharmacy teachers and motivated the women pharmacy teachers to come ahead and contribute in APTI functioning. The Rajasthan APTI officials also graced the inauguration ceremony. The day one inaugural program was coordinated by Dr. Rashmi Trivedi while vote of thanks was proposed by Dr. Pallavi Ahhirao.

The two days intensely thought-provoking sessions by two different renowned resource persons became the strong take away for the delegates. On the first day of conclave, resource person Dr. Vijayalakshmi Suvarna, Managing Director, Liberation coaches Pvt. Ltd known for real time, forthright, no-nonsense solutions to complex people problems conducted the session. She engaged the delegates and explained the difference between Passion, Profession and Purpose through the exercise book: 23 elements to skill development that provided vivid vision to the participants. On second day resource person, Mr. Michael David, founder, Communication Programs, certified cross-cultural trainer and coach, equipped individuals with techniques to manage and resolve conflicts that may arise due to professional differences, promoting collaboration and harmony in the organization as well as within. His activity-based sessions on team spirit, good communication and lesson on "Me, Thee and We" caught the attention of all delegates.

The APTI Women Forum also hosted a Gala Dinner in Rajasthani manner where 50 women delegates, all adorned in folk and traditional Rajasthani attire, were a symbol of vibrant celebration of culture, elegance, and camaraderie. The Delegates were treated to mesmerizing performances of traditional Rajasthani dance forms such as Ghoomar, Kalbelia, and Bhavai. Amidst the Rajasthani colors, flavors, and music the delegates had the opportunity to interact, network and forge meaningful connections, sharing stories and experiences against the backdrop of Udaipur's timeless beauty.

The residential retreat ended with the felicitation of the organisers and delegates, distribution of certificates, mementos, Rajasthani gifts and collecting feedback from all delegates. The ceremony ended with a motivational song by Dr Suneela Dhaneshwar, Director, Amity Institute of Pharmacy, Amity University, Navi Mumbai. Program concluded by the vote of thanks that was proposed by Dr. Udichi Kataria.

The event was supported generously through sponsorship by Indoco remedies Ltd, Naprods Life Sciences, Mayon's Pharmaceuticals, Nagpur, Vicco Laboratories.

This event was convened by Prof. Vandana Patravale, National Convenor, APTI Women's Forum and coordinated by Dr. Pallavi Ahirrao, Dr. Rashmi Trivedi and Dr. Udichi Kataria.

As the delegates departed from Udaipur, they carried with them not only cherished memories of the conference but also renewed inspiration to drive positive change in their respective spheres. The success of the conference underscored the significance of collaborative efforts in advancing the cause of women's empowerment and leadership.

APTI Forum News

1. Participation and representation in the 77th World Health Assembly in Geneva by Dr. Manjiri Gharat

Manjiri Gharat, India is Vice-principal at Prin.K.M.Kundnani Pharmacy Polytechnic, Ulhasnagar,India, Vice-President and Chairperson, Community Pharmacy Division of Indian Pharmaceutical Association (IPA) and Executive Council Member, Community Pharmacy Section of International Pharmaceutical Federation (FIP)2012-16. The advocacy focused on emphasizing the critical role of pharmacy within the health system.

2. Prof. Kamla Pathak honored with Women Scientist Award at International Conference in Dubai

Prof. Kamla Pathak, the esteemed Dean and Professor at the Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences (UPUMS), Etawah, has been awarded the prestigious Women Scientist Award. This recognition was presented by PRISAL during the International Conference on Shaping the Future through Implementation of Advanced Technologies, held on April 20-21, 2024, in Dubai, UAE.

Prof. Pathak's dedication to the field of pharmacy and her innovative contributions have significantly advanced pharmaceutical sciences. Her work has not only elevated the standards of education and research at UPUMS but has also made a substantial impact on the global stage.


Women Scientist award 2024

3. Celebrating academic excellence: Prof. Kamla Pathak surpasses 10,000 citations milestone

Prof. Kamla Pathak, the esteemed Dean and Professor at the Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences (UPUMS), Etawah, has reached a significant milestone in her illustrious career by surpassing 10,000 citations for her impactful research contributions.

Prof. Pathak's journey in the realm of pharmaceutical sciences has been marked by dedication, innovation, and a relentless pursuit of excellence. Her pioneering work spans diverse areas including modulated/targeted drug delivery systems and product development, addressing critical challenges in healthcare with ingenuity and precision.

4. Dr.Pearl Dighe clinches second position in national seminar's oral presentation competition

Dr. Pearl Dighe, Associate Professor at PES's Rajaram & Tarabai Bandekar College of Pharmacy, Goa, has brought laurels to her career by securing the second position in the Oral Presentation Competition. Her presentation, titled "The Role of Intellectual Property Law in Protecting Cosmetic Formulation: A Review," captivated the audience and impressed the jury at the Madhya Pradesh Council of Science and Technology sponsored two-day National Seminar at Acropolis Institute of Pharmaceutical Education and Research, Indore, from April 19th to 20th, 2024 on "Patents and IPR: A Roadmap for Technological Advancement."

5. Dr. Pallavi Ahirrao Jachak elevated to professorship at Chandigarh Group of Colleges

Dr. Pallavi Ahirrao Jachak has been promoted to the esteemed position of Professor at Chandigarh Group of Colleges, effective from April 1st, 2024. Dr. Jachak's promotion is a testament to her exemplary dedication, scholarly achievements, and contributions to academia. Her vast experience, coupled with her passion for research and education, has earned her the respect and admiration of colleagues and students alike.


Chandigarh Group of Colleges

Ref. No.:- CGC/2024/37 Dated: April 19, 2024

To,
Dr. Pallavi Ahirrao Jachak
Associate Professor
Pharmacy
Chandigarh College of Pharmacy

Subject: Promotion Letter

Dear Dr. Pallavi Ahirrao Jachak ,

We have pleasure in informing you that in appreciation of your overall performance the Management has decided to promote you as Professor with effect from April 1, 2024.

In the capacity of Professor, we expect you to continue to maintain high standards of discipline, efficiency and integrity.

Please accept our heartiest congratulations on this well-deserved recognition of your continuing excellent contributions and commitment towards CGC. For our record, please return a copy of this letter duly accepted and signed by you.

All other terms and conditions of your appointment remain unchanged.

Barinder S.Sawhney
Director-HR

6. Dr. Vandana Patravale honored as keynote speaker at International Health Sciences Conference

Dr. Vandana Patravale, esteemed Professor of Pharmaceutics at the Institute of Chemical Technology (ICT), Mumbai, was bestowed with a prestigious honor as she graced the International Conference on Recent Advances in Health Sciences - 2024 at Lovely Professional University (LPU) as speaker. Dr. Ashok Kumar Mittal, Member of Parliament, Rajya Sabha, and Chancellor of LPU, extended a warm felicitation to Dr. Patravale, recognizing her as a distinguished keynote speaker.

7. Dr. Vandana Patravale received Best Faculty Award

Dr. Vandana Patravale, Professor of Pharmaceutics at the Institute of Chemical Technology (ICT), Mumbai, received the prestigious "Best Faculty Award." This accolade was a testament to her exceptional teaching prowess and dedication to nurturing the minds of students. The recognition was conferred based on evaluations by the final year B. Pharm. class for the academic year 2023-24, highlighting Dr. Patravale's exemplary contributions to education and her profound impact on the learning journey of her students.


INSTITUTE OF CHEMICAL TECHNOLOGY

Best Teacher Award

This is to certify that *Professor V. B. Patravale* bestowed with the "*Best Teacher Award*" on the basis of evaluation by the Final Year B. Pharm. class for her excellent teaching skills during 2023-2024.

Professor A.B. Pandit
Vice Chancellor

Date: April 20, 2024

8. Dr. Pooja A Chawla invited as resource person at International Health Sciences Conference at LPU

Dr. Pooja A Chawla, distinguished Professor at the University Institute of Pharmaceutical Sciences and Research, Baba Farid University of Health Sciences, Faridkot, was accorded invitation to serve as a Resource Person at the International Conference on Recent Advances in Health Sciences, hosted by Lovely Professional University (LPU).

The International Conference on Recent Advances in Health Sciences stands as a pinnacle event in the realm of health sciences, bringing together luminaries, scholars, and practitioners from across the globe to deliberate on the latest advancements and innovations in healthcare.

9. Ms. Rakhi Khabiya successfully organized MPCST sponsored National Seminar as convenor

The National Seminar on "Patents and Intellectual Property Rights: A Roadmap for Technological Advancement," sponsored by the Madhya Pradesh Council of Science and Technology (MPCST), was successfully organized on April 19th-20th, 2024. Ms. Rakhi Khabiya, serving as the Convenor of the seminar, spearheaded the event's coordination and execution.

The Chief Guest of the seminar was Dr. Vishwajanani Sattigeri, Head, CSIR-Traditional Digital Library Unit and Guest of Honor was Dr. Yogesh Bajaj, Deputy Controller of Patents and Design, Indian Patent Office, Mumbai. The speakers were Dr. Sheetal Chopra, Director and India Lead, IPR Policy, Ericsson India and Founder India International IP Forum, Mr. Vijay Kumar Shivpuje, Director Patlex Business Solutions and Pharmaliterati and Mr. Gaurav Phadnis, Associate Partner, Patent and Trademark, Lexorbis.

The seminar featured plenary talks, workshops on patent claim drafting, e-poster presentations focusing on intellectual property rights (IPR) and pharmaceutical themes, quiz competitions centered on IPR for students, and oral presentations by faculties on IPR themes. Total 332 delegates registered for the event, 130 e-poster were presented, and 24 teams participated in the quiz. The seminar witnesses participation from 13 states covering 64 cities of India.

10. Ms. Rimjhim Arora, PhD, BN University, Udaipur received the Best Young Researcher award

Ms. Rimjhim Arora received her doctorate from BN University, Udaipur. Her research topic was 'In-silico screening of various compounds for the treatment of Alzheimer's disease'. This research was guided by Dr. Kamal Singh Rathore, Professor of Pharmaceutics, BN College of Pharmacy, Udaipur. As a result of this unique research, Rimjhim has presented her papers in local and international conferences, providing the society with direction towards the treatment of Alzheimer's disease. Her diligence and ethics have earned her this honour. During this period, she received the Best Young Researcher Award as well as many other awards. Rimjhim is life member of varios professional bodies like APTI, APTI women Forum, IPGA etc.

11. Women's Day celebration at Smriti College of Pharmaceutical Education

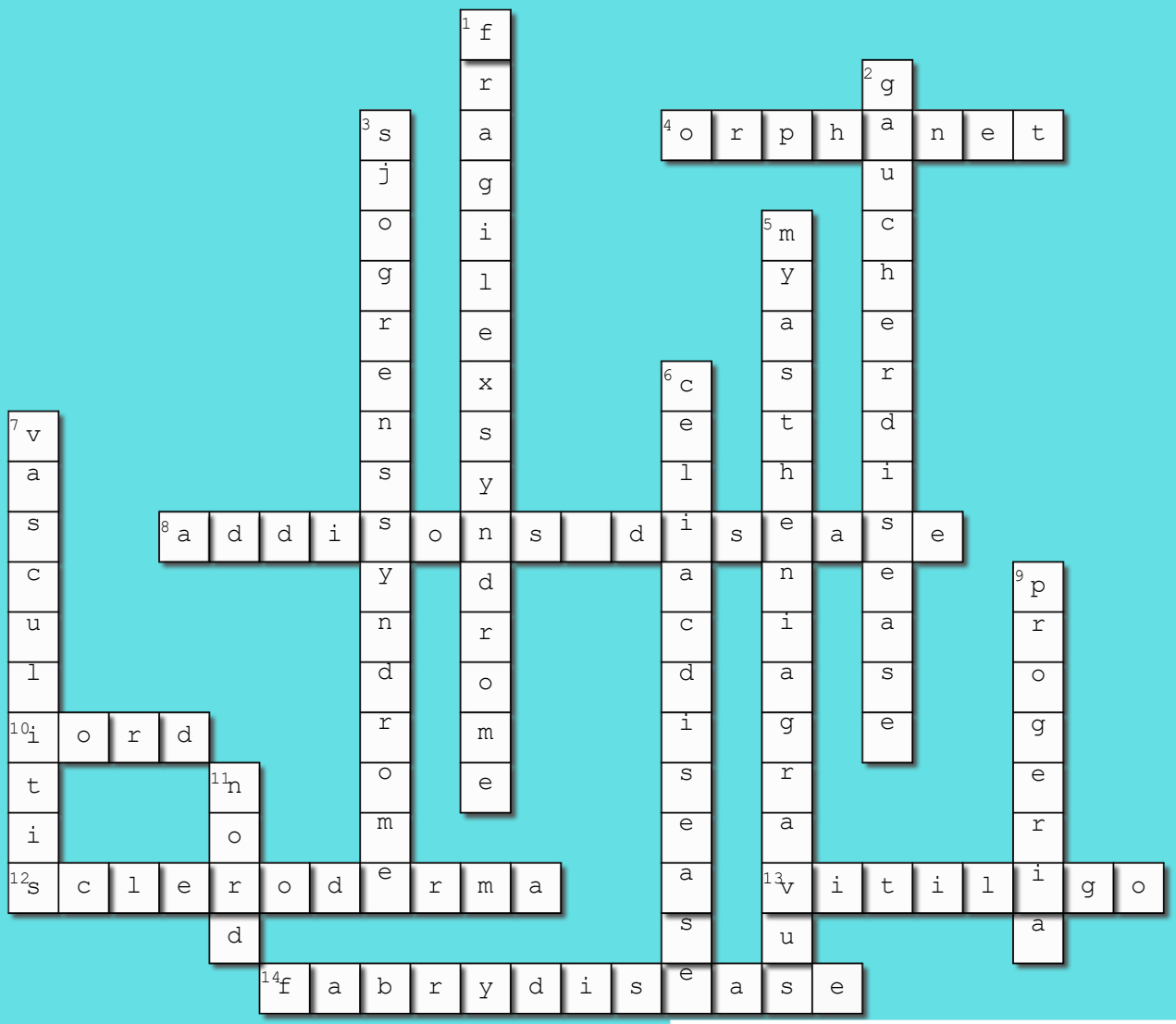
Smriti College of Pharmaceutical Education Celebrated Women's Day with great Enthusiasm Principal Dr. Neelesh Malviya welcomed the guests, Lieutenant Colonel Reenu Tanwar and Gynaecologist Dr. Ashtha Jain Mathur. Lieutenant Colonel Reenu Tanwar addressed the students with insights from her military experience, emphasizing resilience, leadership, and breaking barriers. She also mentioned that in addition to having financial stability, today's women should also be financially literate and independent. Dr. Ashtha Jain Mathur shed the light on this year's concept of international Women's Day "BREAK THE BIAS". She gave the young women insights on various prevailing health issue and lifestyle disorders. Cake cutting was done followed by a series of fun activities specially curated for the occasion. The event served as a reminder of the power of unity and solidarity in advancing the cause of gender equality, both within the college campus and in society at large.

12. International Women's Day celebration at College of Pharmaceutical Sciences at Dayananda Sagar University

The College of Pharmaceutical Sciences at Dayananda Sagar University celebrated International Women's Day with great enthusiasm on March 26, 2024, at the CD Sagar Auditorium, with the theme "Invest in Women, Accelerate Power". The Women's Cell Convener and Coordinator, Dr. Geetha KM, welcomed the gathering. Dr. N.M. Raghavendra, Principal, COPS gave the opening remarks about gender equality and women empowerment. Dr. Tejaswini Anant Kumar, Chairman and Co-Founder of the Adamya Chetana Foundation, Bengaluru shared innovative waste management strategies while Mrs. Nalini Shekar, Executive Director and Co-Founder of Hasiru Dala, Bengaluru emphasized the importance of waste management and her organization's empowering initiatives. Mrs. Kumuda, operator and entrepreneur of the DWCC, enlightened the audience on her journey from a waste picker to an entrepreneur by empowering individuals economically and fostering a sense of community and collaboration. Dr. Pushpa Sarkar, Dean, SHS in her presidential address, celebrated the outstanding contributions of women invitees, setting a tone of appreciation. The celebration concluded with a gracious vote of thanks by Dr. Kalpana Divekar, expressing gratitude to all who had contributed to the success of the event.

Name:_____

Complete the crossword puzzle below



Across

4. Database of information on rare diseases and orphan drugs for all publics (orphanet)
8. Rare disease associated with adrenal glands (addisons disease)
10. Indian Organization for Rare Diseases (iord)
12. Rare autoimmune disorder causing abnormal skin thickening (scleroderma)
13. Rare skin condition (vitiligo)
14. Rare Lysosomal Storage Disease (fabrydisease)

Down

1. Rare hereditary disorder that causes mental retardation (fragilexsyndrome)
2. Rare Disease associated with deficiency of glucocerebrosidase enzyme (gaucherdisease)
3. Rare autoimmune disorder involving lymphocyte (sjogrenssyndrome)
5. Rare autoimmune disorder affecting muscles (myastheniagravus)
6. Rare gluten disorder (celiacdisease)
7. Rare disease involving inflammation of blood vessels (vasculitis)
9. Rare aging related disease (progeria)
11. Group of leading companies committed to helping people with rare diseases (nord)

Name:_____

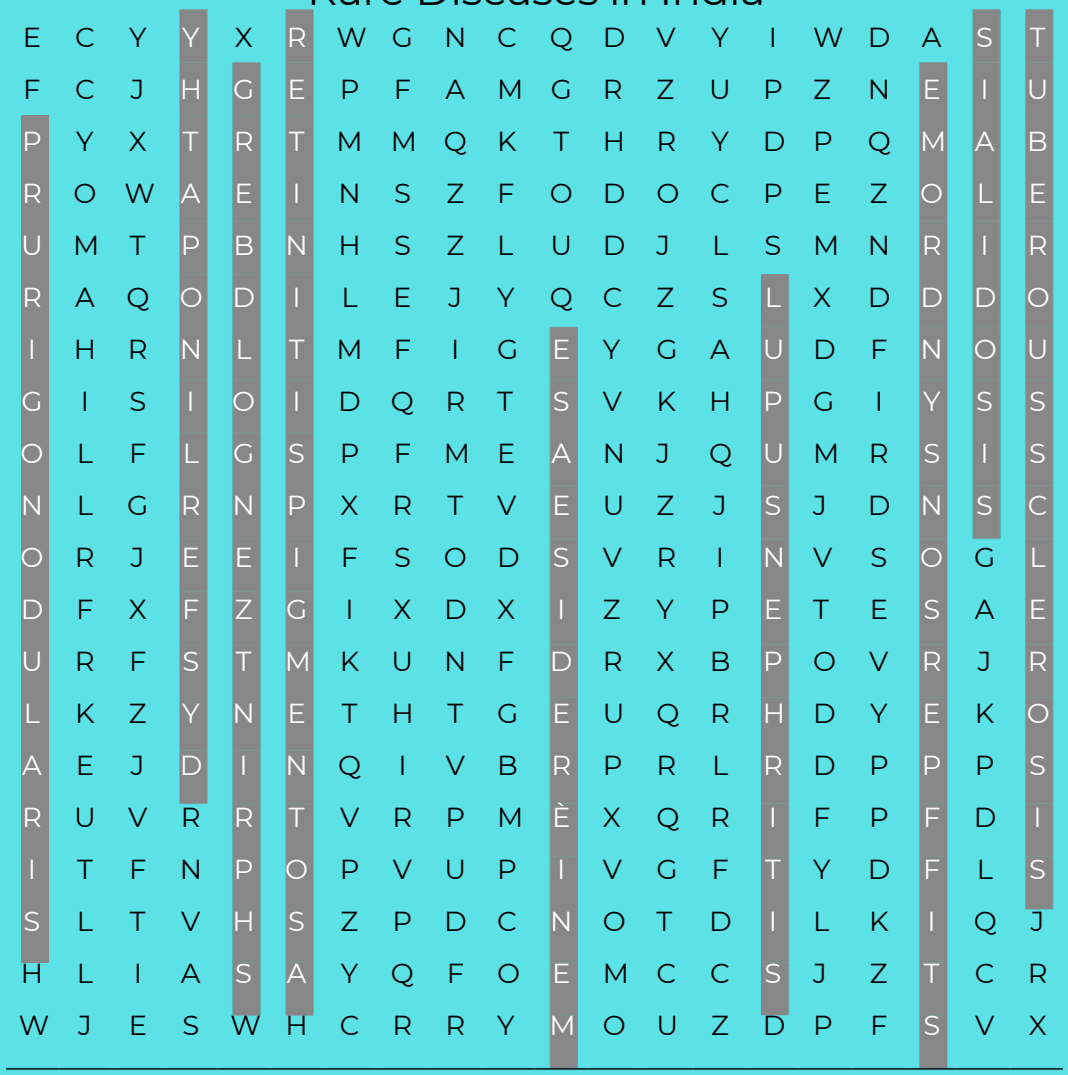
Rare Diseases in India

Please unscramble the words below

1. yaoamFrgibli	Fibromylagia	a disorder characterized by widespread musculoskeletal pain
2. iaxatA	Ataxia	disease without coordination
3. oryucehHdlaps	Hydrocephalus	an abnormal buildup of cerebrospinal fluid in the ventricles
4. osoiilAsdmy	Amyloidosis	rare disease associated with amyloid buildup
5. narlrmeBlSGradoiyunei	GuillainBarreSyndrome	rare autoimmune disorder affects the nerves

Name: _____

Rare Diseases in India



DYSFERLINOPATHY
LUPUSNEPHRITIS
MENIèREDISEASE
PRURIGONODULARIS
RETINITISPIGMENTOSA
SHPRINTZENGOLDBERG
SIALIDOSIS
STIFFPERSONSYNDROME
TUBEROUSSCLEROSIS

PUBLISHED BY: Secretary APTI, on behalf of APTI

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Phone : 9945846106,+91 90088 88415

LOTUS LOGO STORY

As a lotus is able to emerge from muddy waters un-spoilt and pure it is considered to represent a wise and spiritually enlightened quality in a person; it is representative of a woman who carries out her tasks with little concern for any reward and with a full liberation from attachment. Lotus-woman in the modern sense of women's qualities: she is superbly intelligent, highly educated, and totally committed to individualism. She is politically astute and works incessantly for a better and more humane society. She is exquisite in her taste for music, art and culture, abounds in social graces and performs brilliantly in communication.