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.

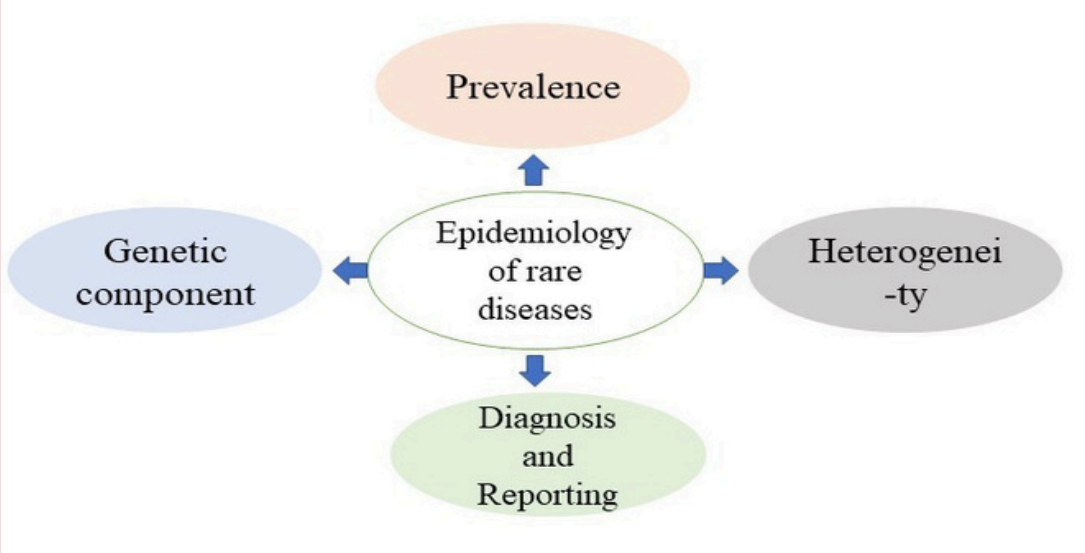

Figure 1. Epidemiology of rare diseases

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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