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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