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Review Article

Review On : Orphan Diseases And Treatment

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ABSTRACT

Rare diseases are individually rare but globally affect around 6% of the population, and in over 70% of cases are genetically determined. Their rarity translates into a delayed diagnosis, with 25% of patients waiting 5 to 30 years for one. Living with a rare disease is a challenge and the lack of diagnosis -either because one exists but has not been identified for a particular patient or because the patient has a "syndrome without a name" (SWAN) -is a cause of extreme stress for patients and their families. A recent calculation of the cumulative prevalence at a global level based on the Orphanet epidemiology data file estimates that, regarding the 2017 population, there is a minimum prevalence of 3.5–5.9% affected worldwide. The problem is that each of those patients has a condition that they share with only a small number of individuals locally and sometimes even globally. For this reason, it is difficult to ensure that patients can access the right medical expertise as doctors seldom see such cases, and this fact contributes to a delay in diagnosis. It is essential to raise awareness of patients and clinicians of existing gene and variant-specific therapeutics at the time of diagnosis to avoid that treatment delays add up to the diagnostic odyssey of rare diseases' patients and their families.

INTRODUCTION

The word orphan comes from the Greek word orphanos, a child who has lost one parent or both, or an adult who has lost a child. It goes back to the putative IndoEuropean root ORBH, bereft, as in the Latin word orbus. The obsolete English words orbation and orbity meant orphanhood or childlessness. One who is bereft of freedom is a slave, made to work hard – consider the words for work in some modern European languages, such as the German Arbeit and the Czech robota. In his 1920 play R.U.R. (Rossum's Universal Robots) Karel apek introduced the word robot (female robotka) for an imagined race of mechanical men and women. The etymology reminds us of the link between orphans and the workhouse. According to World Health Organization (WHO), a rare disease is defined as debilitating lifelong disease or condition with a prevalence of ≤ 1 per one 1

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thousand population.[1] Different countries (developed and developing) have different definitions of rare disease according to suitability of their own requirements. Because of this reason, heterogeneity exists in the definition of rare disease and no consensus exists amongst various nations. Rare diseases, in actual, are not that much rare at all. In fact, if we go by the words of National Institutes of Health (NIH), out of total American population, 30 million have one of the nearly 7,000 diseases that are officially declared "rare". According to Europe, orphan diseases are defined as those disease affecting less than 1 in 2000 population, whereas, in USA, rare disease is defined as disease which affects less than 2,00,000 people at a certain point of time.[2] Ultra rare disease is defined as that disease that includes less than two patients per one lakh population.[3] The term orphan disease implies two separate but related concepts. It has been used to describe diseases that are neglected by doctors, and has been applied, for example, Fabry's disease, alveolar echinococcosis, variant renal cancer, high myopia, and even some common conditions, such as endometrial cancer and tobacco addiction. However, more specifically the term orphan disease is used to designate diseases that affect only small numbers of individuals (so-called health orphans).[4] There is no satisfactory definition of an orphan disease. In the USA it is defined as one that affects fewer than 200 000 individuals, but in Japan the number is 50000 and in Australia 2000.[5] These numbers clearly relate to the population sizes of these countries, but even adjusting for that, the definitions vary from about 1 to 8 in 10 000. The European Community definition is less than 5 in 10 000. The WHO has suggested a frequency of less than 6.5–10 in 10 000, although that seems rather high. There are also lists of diseases, mostly genetic disorders, that are regarded as being rare. As a group they have nothing in common apart from their rarity, but the lists vary strikingly in length; for example, that published by the US National Organization for Rare Disorders contains about 1200 items,[6] while NIH's Office of Rare Diseases publishes a list of over 6000, ranging from Aagenaes syndrome (lymphoedema and intrahepatic cholestasis) to Zuska's disease (lactiferous fistulae of the breast)[7]. An orphan drug can be defined as one that is used to treat an orphan disease. For example, haem arginate, used to treat acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria,[8] is an orphan drug. However, it comes as a surprise that ibuprofen can also be categorized as an orphan drug, because it has been used to treat an orphan disease, namely patent ductus arteriosus in neonates (whether orphans or not). This observation stresses that barriers to the development of orphan drugs do not occur only at the premarketing stage; in some cases, it may not be commercially worth mounting an efficacy trial, even of a drug whose efficacy elsewhere is well established. Indeed, there may be little incentive to mount an efficacy trial of a well-established drug in a rare condition, or even in a relatively common condition in a subgroup of individuals – consider the many drugs that are licensed for use in adults but not in children. In the last 20 years efforts have been made to encourage companies to develop orphan drugs. The Orphan Drug Act in the USA (1983) was succeeded by similar legislation in Japan (1985), Australia (1997), and the European Community (2000)[5]. The encouragement takes three forms: tax credits and research aids, simplification of marketing authorization procedures, and extended market exclusivity[5 9]. In Europe only the last is available. The World Health Organization defines orphan/rare diseases as, 'all pathological conditions that affect 0.65-1 out of every 1000 inhabitants'. The EU defines a rare disorder as one with a prevalence of 5: 10,000 Europeans; the USA accepts it as an ailment affecting fewer than 2,00,000 Americans (with an incidence of less than 1/5,000 in the general

population); Japan has the limit at 50,000 Japanese patients and Australia at 2000 Australian patients.[10] There are approximately 6,000 orphan diseases, out of which 80% are genetic.[11] These diseases are very much like children without parents and as such, require special effort for the development of their treatment options. But they are usually not studied for their pathophysiology or for newer therapeutic options,[12] as the inputs are not economically rewarding. Hence, treatment and diagnostic methods also have not yet been fully developed for them. Many orphan diseases are lesser known, like Juberg Marsidi syndrome (a genetic disorder of childhood that leads to severe mental retardation, abnormal bone growth resulting in the disfiguring of the head and body and loss of hearing), Werdnig Hoffman disease (a fatal, fetal disease similar to amyotrophic lateral sclerosis (ALS), Omenn's syndrome (absence of mature B and T cells, children being born with late-stage ALS-like symptoms), Fabry's disease (an X-linked lysosomal-storage disorder due to deficiency of galactosidase A), Lambert-Eaton myasthenic syndrome (an autoimmune disease of peripheral cholinergic system resulting in muscle weakness due to impaired acetylcholine release) and many more like Aarskog syndrome, Adams Nance syndrome, Bagatelle Cassidy syndrome, Bamforth syndrome, Ballard syndrome and Bahemuka Brown syndrome. There are some familiar orphan/rare/neglected diseases, like Alzheimer's disease, ALS , Crohn's disease, Hodgkin's disease, leukemia (many forms), multiple sclerosis, Huntington's disease, sickle cell disease, muscular dystrophy, myasthenia gravis and spinal cord injury . All disorders due to genetic defects in development (like spina bifida, Turner's syndrome, Klinefelter's syndrome, cleft lip and palate) and deficient enzymes (like cystic fibrosis, respiratory distress syndrome, Gaucher's disease, hemophilia), are considered orphan diseases. Tropical infectious diseases like malaria, leprosy, tuberculosis and leishmaniasis with lesser incidence in developed countries, may also be considered as orphan diseases there.

(1) Addison's Disease: Addison disease is an acquired primary adrenal insufficiency. A primary adrenal insufficiency is termed Addison disease when an autoimmune process causes the condition. It is a rare but potentially life-threatening emergency condition. The most common cause of primary adrenal insufficiency is autoimmune adrenalitis (Addison disease), associated with increased levels of 21-hydroxylase antibodies[13] [14]. the main cause of Addison's disease. When the gland is damaged, it does not release sufficient amount of cortisol or aldosterone which cause this disease.[15] Common signs and symptoms observed for adrenal insufficiency are as Extreme tiredness, Loss of appetite and weight loss, Hyperpigmentation of skin (darkening) on knuckles, elbows, toes, lips, Weakened muscles, joint pain and abdominal pain, Low blood pressure and low blood glucose condition (Hypoglycemia), Behavioral symptoms-depression, irritation, craving for salty foods, Gastrointestinal problems-nausea, vomiting, diarrhea.

Pathophysiology: Adrenal failure in Addison disease results in decreased cortisol production initially followed by that of aldosterone, both of which will eventually result in an elevation of adrenocorticotropic (ACTH) and melanocyte-stimulating hormone (MSH) hormones due to the loss of negative feedback inhibition.[16]

Treatment: Early recognition is critical for the management of adrenal insufficiency. Addison crisis is a severe endocrine emergency; immediate recognition and treatment are required. Beware that if not recognized and treated, the adrenal crisis can be fatal. The confirmatory laboratory evaluation should not delay the treatment. Blood samples should be obtained for subsequent measurement of ACTH and cortisol levels.

Diagnosis: The differential diagnosis of adrenal crisis includes most other conditions that can cause shock. The differential diagnosis of adrenal insufficiency is broad. Some common differential diagnoses are discussed here.

- **Sepsis**: Many features of sepsis overlap with adrenal insufficiency. The presentation includes weakness, fatigue, vomiting, hypotension, and shock. The confirmation of primary adrenal insufficiency diagnosis is made by low cortisol response to ACTH stimulation test and low ACTH level.
- **Shock** (due to any cause): Plasma cortisol level with shock suggests adrenal insufficiency.
- **Chronic Fatigue Syndrome**: Chronic persisting or relapsing fatigue may mimic adrenal insufficiency. However, laboratory evaluations such as cortisol level after corticotropin stimulation differentiate it from adrenal insufficiency.
- **Infectious Mononucleosis:** The presentation may be similar to fever, fatigue, and myalgias may occur in both conditions. However, exudative pharyngitis is present in this condition. IgM antibodies to viral capsid antigen are present.
- **Hypothyroidism**: As with adrenal insufficiency, fatigue may be present in hypothyroidism. However, it is associated with weight gain. The cortisol level should differentiate both conditions.[17]

(2) Angelman Syndrome: AS is a rare genetic neuro-developmental disorder characterized by severe developmental delay, sleep disorders, jerky movements and frequent laughter. It was first discovered in the year 1965 by a British Pediatrician, Dr. Harry Angelman.The syndrome is caused by an abnormality in a region of chromosome 15 and it's usually not recognized at birth. AS is typically diagnosed between the ages of 3 and 7. The main characteristics of this syndrome are delayed motor skills, minimal or absence of speech, developmental delay, ataxia (shaky and unsteady movements), seizures, constant happy behavior that includes frequent laughing, smiling and excitability. The exact prevalence of AS is unknown, but it is estimated that it affects 1 in 12000-20000 people. Common signs and symptoms observed for Developmental delays usually noticeable between 6 to 12 months , In addition to this there may be sucking difficulties and problems with feeding, lack of crawling or babbling , Seizures are reported in 80% of cases.

Diagnosis and Testing

- The diagnosis and testing of AS is usually carried out after the baby is born.
- A blood test can detect most of the individuals with AS by identifying whether the UBE3A gene is functioning properly or not.
- Fluorescent in situ hybridization (FISH) test.
- CGH Array test.

Treatment:

- As for now, there is no cure available for AS. But through various types of therapies, the life of an AS individual can be made much simpler.
- Occupational Therapy.
- Physiotherapy
- Communication and Speech Therapy.
- Use of anti-convulsion medication.
- Medication for sleep disorder
- Regular eye check up[18]

(3) Progeria:

Progeria (also known as "Hutchinson–Gilford progeria syndrome", "Hutchinson–Gilford syndrome", and "Progeria syndrome") is an extremely rare genetic condition wherein symptoms resembling aspects of aging are manifested at an early age. The word Progeria comes from the Greek progeros meaning 'prematurely old'. The Greek word pro means

'before', while the word geras means 'old age'. The disorder has very low incidences and occurs in one per 8 million live births. The earliest symptoms include failure to thrive and a localized scleroderma-like skin condition. As a child ages past infancy, additional conditions become apparent. Limited growth, alopecia, and a distinctive appearance (small face and jaw, pinched nose) are all characteristic of progeria. People diagnosed with this disorder usually have small, fragile bodies, like those of elderly people. Later, the condition causes wrinkled skin, atherosclerosis, and cardiovascular problems. Hutchinson-Gilford progeria syndrome (HGPS) is a childhood disorder caused by a point mutation in position 1824 of the LMNA gene, replacing cytosine with thymine, creating an unusable form of the protein Lamin A. Lamin A is part of the building blocks of the nuclear envelope.[19]

Diagnosis: Diagnosis is suspected according to signs and symptoms, such as skin changes, abnormal growth, and loss of hair. It can be confirmed through a genetic test.

Treatment:

- No treatments have been proven effective. Most treatment focuses on reducing complications (such as cardiovascular disease) with heart bypass surgery or low-dose aspirin. Children may also benefit from a high-calorie diet.
- Growth hormone treatment has been attempted.
- A type of anticancer drug, the farnesyltransferase inhibitors (FTIs), has been proposed, but their use has been mostly limited to animal models. A Phase II clinical trial using the FTI Lonafarnib began in May 2007.

Prognosis:

- There is no known cure. Few people with progeria exceed 13 years of age. At least 90% of patients die from complications of atherosclerosis, such as heart attack or stroke.
- Mental development is not affected. The development of symptoms is comparable to aging at a rate eight to ten times faster than normal, although certain age-related conditions do not occur. Specifically, patients show no neurodegeneration or cancer predisposition. They do not develop physically mediated "wear and tear" conditions commonly associated with aging, like cataracts (caused by UV exposure) and osteoarthritis (caused by mechanical wear).
- Although there may not be any successful treatments for progeria itself, there are treatments for the problems it causes, such as arthritic, respiratory, and cardiovascular problems.

(4) Crohn's Disease: Inflammatory bowel disease (IBD) results from the interaction between genetic and environmental factors which influence the immune responses. Inflammatory bowel diseases are mainly divided into **ulcerative colitis (UC) and Crohn's disease (CD)**. Crohn's disease is similar to UC, both of which have been classified as chronic IBD and which cause digestive disorders and inflammation in the gastrointestinal tract. Some of the symptoms of CD and UC include diarrhea, abdominal pain, rectal bleeding, and weight loss. They are mainly characterized by inflammation. Both the diseases may occur in adolescents and adults and affect men and women equally[20]. Despite the similarity between the symptoms of these two diseases, there are some differences between the symptoms of CD and UC. Crohn's disease is one of the IBDs that occur in patients between ages 15-35 years. Unlike other inflammatory diseases, IBDs could not be suppressed easily. Consequently, the immune system is stimulated, and part of the intestine is destroyed. It causes pain, diarrhea, fever, and other symptoms. In addition to the serious effect on the

lower part of the small intestine, CD can also occur in parts of the digestive tract including the large intestine, stomach, esophagus, or even mouth[21]. Crohn's disease affects the mouth, anus, and the entire layers of the intestine. Ulcerative colitis affects the mucosal layer of the colon. The lesions occur in the rectum and the intestine. The symptoms are mild to severe and may threaten life[20]. The symptoms of CD and UC are very similar. Malnutrition is very common in CD because the small intestine is responsible for the absorption of nutrients, and CD damages the small intestine[22]. the disease is active, symptoms typically include: Diarrhea,Fever, Fatigue, Abdominal pain and cramping, Blood in your stool, Mouth sores, Reduced appetite and weight loss, Pain or drainage near or around the anus due to inflammation from a tunnel into the skin (fistula). Other signs and symptoms are People with severe Crohn's disease may also experience symptoms outside of the intestinal tract, including Inflammation of skin, eyes and joints, Inflammation of the liver or bile ducts, Kidney stones, Iron deficiency (anemia), Delayed growth or sexual development, in children.

Causes: The exact cause of Crohn's disease remains unknown. Previously, diet and stress were suspected, but now doctors know that these factors may aggravate, but don't cause, Crohn's disease. Several factors likely play a role in its development.

Immune system - It's possible that a virus or bacterium may trigger Crohn's disease; however, scientists have yet to identify such a trigger. When your immune system tries to fight off an invading microorganism or environmental triggers, an atypical immune response causes the immune system to attack the cells in the digestive tract, too.

Heredity -Crohn's disease is more common in people who have family members with the disease, so genes may play a role in making people more likely to have it. However, most people with Crohn's disease do not have a family history of the disease.

(5) Fabry Disease:

Fabry disease is a rare genetic disorder that is caused due to the deficiency of an enzyme called α-galactosidase A (α-Gal A). It is caused by mutations in the GLA gene. This gene is in turn responsible for providing instructions for the formation of α-Gal A enzyme. Fabry disease (also known as Fabry's disease, Anderson-Fabry disease, angiokeratoma corporis diffusum and alpha-galactosidase A deficiency) is a rare X-linked recessive (inherited) lysosomal storage disease, which can cause a wide range of systemic symptoms. The disease is named after one of its discoverers, Johannes Fabry. Fabry's disease (FD) is one of those rare disorders which are highly undiagnosed. The reported incidence of this disorder is 1/40,000 males.[22] [24] FD being a rare cause of end-stage renal disease (ESRD), accounts for 0.0167% of all causes of ESRD.[23]

Other names for this condition

- alpha-galactosidase A deficiency
- Anderson-Fabry disease
- Angiokeratoma Corporis Diffusum
- Angiokeratoma Diffuse
- Ceramide Trihexosidase Deficiency
- GLA deficiency
- Hereditary Dystopic Lipidosis

Symptoms: Pain and Acroparesthesia- Pain is an early symptom and may occur as early as 2-8 years of age. Affected individuals may experience episodes of severe burning pain in the hands and the feet (**acroparesthesia**). Severe episodes of pain (Fabry's **crises**) may last for hours to days and are frequently triggered by exercise, fatigue, stress, and/or fever.

Anhidrosis or Hypohidrosis- Type 1 males and some type 1 females have decreased or absent sweat production (hypohidrosis or anhidrosis).

Gastrointestinal problems- Abdominal cramping, frequent bowel movements, and

diarrhea may also occur, particularly after a large meal.

Other symptoms- Chronic fatigue, dizziness, headache, generalized weakness, nausea, and/or vomiting, delayed puberty, lack of or sparse hair growth, and rarely malformation of the joints of the fingers. Ear damage and progressive organ damage (especially kidney and heart).

Causes: In Fabry disease, the production of an enzyme called alpha-galactosidase A is affected. This enzyme is active in lysosomes, which are structures that serve as recycling centers within cells. Alpha-galactosidase A normally breaks down a fatty substance called globotriaosylceramide. Mutations in the GLA gene alter the structure and function of the enzyme, preventing it from breaking down this substance effectively. As a result, globotriaosylceramide builds up in cells throughout the body, particularly cells lining blood vessels in the skin and cells in the kidneys, heart, and nervous system.

Diagnosis:

- Genetic Testing: Preimplantation (embryo before uterine implantation) genetic diagnosis is available when the familial mutation in the GLA gene is known.
- Chronic Villus Sampling is a prenatal test that is used to detect birth defects, genetic diseases, and other problems during pregnancy. During the test, a small sample of cells (called chorionic villi) is taken from the placenta where it attaches to the wall of the uterus. Early prenatal diagnosis at about 10 weeks of pregnancy can be made by α-Gal A enzyme and GLA mutation analyses of villi obtained by chronic villus sampling, or by amniocentesis at about 15 weeks of gestation.
- Clinical Diagnosis of type 1 classic phenotype can be made clinically by physicians who recognize the characteristic findings of episodic pain in the extremities, absent or decreased sweating (anhidrosis or hypohidrosis), typical skin lesions (angiokeratoma), gastrointestinal abnormalities, and the corneal dystrophy in childhood or adolescence.
- Newborn screening studies have identified affected males by demonstrating the reduced α-Gal A activity in dried blood spots followed by GLA gene sequencing.

Treatment: Major treatment followed is the Enzyme Replacement Therapy. It is the treatment that replaces an enzyme that is deficient or absent in the body. Usually given as intravenous infusion or injection. In the case of Fabry disease Agalsidase-alpha or Agalsidase- beta is given to help normalize kidney function, heart function, and blood supply to the brain. Symptomatic treatment includes medications for neuropathic pain, hearing aid in case of hearing loss, medications for nausea, and vomiting. Other later complications (e.g., kidney failure or heart problems) should be treated symptomatically after consultation with a physician who is experienced in the care of patients with Fabry disease. Genetic counseling is recommended for affected individuals and their families.

Discussion: About 80 percent of rare diseases are believed to be genetic in origin, while 70 percent start in childhood. About 9 percent of Southeast Asia's population suffer from them. The cultural practice of consanguineous marriages is believed to be one of the reasons for the high prevalence of rare diseases in this region. In India too, endogamy in the north and consanguinity in the south are said to be responsible for many of the rare diseases.

There is no universally accepted definition of rare diseases and the definitions usually vary across different countries. However, the common considerations in the definitions are primarily, disease prevalence and to varying extent - severity and existence of alternative therapeutic options.

Under normal marketing conditions, the pharmaceutical industry lacks incentive to commit

to the high costs associated with developing a new drug for a disease with low prevalence. If the size of the patient population and the expected drug sales are inadequate to cover the return on investment in a new drug, such development would be financially unviable for the industry. In light of this, a rare disease could be defined as one that is not cost effective to treat. Legislative incentives, for example, tax credits, research aids, simplification of the marketing authorization procedures, or extended market exclusivity can be introduced to make developing orphan drugs profitable.

CONCLUSION

The world of rare diseases has changed significantly in the past two decades. Identifying patients, moving ahead with the science, developing new drugs, building international registries and reference networks-all these activities take time and money. As many of the contributors have emphasized, a key problem is the lack of awareness and interest in rare diseases. Understanding of rare diseases, it is hardly surprising that they are low on everyone's agenda. The drug development will take place with aims to develop medicines for orphan diseases and to sell them to the health services at an affordable price in order to take the strain off health budgets and make more treatments available for more people.

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