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# Challenges in the Diagnosis and Treatment of Patients with Rare and Orphan Diseases

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## Abstract

Orphan diseases are diverse group of disorders that have not gained much of public attention as they are rarely reported worldwide. The term orphan and rare diseases are often used interchangeably when describing diseases that fall into an orphan or rare category. Around 80% of orphan diseases are chronic, serious, or life threatening, are of genetic origin, and are more prevalent in children and in adults above 40 years of age. Due to rarity, lack of financial support and specific drug to treat these diseases, diagnosis, and treatment becomes challenging. Diagnosis is usually delayed, and patient continues to suffer by seeking multiple specialist opinion. Nonavailability of specific drug and lack of financial funding or waivers to conduct to conduct clinical trial for invention of new orphan drug are the obstacles for targeted treatment. Hence, there is need for comprehensive integrative approach to manage orphan disease patients and pharmaceutical companies should be encouraged for invention of drugs at a reasonable cost for orphan diseases. In addition, community education through genetic-based learning modules is essential to increase awareness of population about risk factors and early diagnosis of orphan diseases, and to take opinion of specific specialist for thorough clinical evaluation. This review discusses challenges faced by the specialists toward diagnosis and treatment of orphan disease for well-being of an individual living with the disorder.

**Keywords**
- orphan diseases
- orphan drug
- rare diseases
- diagnosis

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## Introduction

Orphan diseases are group of diseases that have a low prevalence of less than 6.5 to 10 cases in 10,000 people according to World Health Organization (WHO), and these diseases have not gained much of public attention as they are extremely rare and less reported worldwide.[1] There is no universally accepted definition, and different countries have defined it based on the prevalence, population size, disease severity, and suitability according to the needs. United States defines it as an ailment affecting fewer than 2,00,000 Americans, Japan around 50,000 individuals, Australia 2000 individuals, and India refers it as an ailment affecting less than 50,000 Indian patients.[2,3]

According to US Orphan Drug Act 1983, "rare diseases" might also be termed as an orphan disease that includes various syndromes affecting dental and bone structures such as tricho-dento-osseous syndrome, Tourette's syndrome, McCune-Albright syndrome, and osteogenesis imperfecta. As there is lack of sufficiently large market to obtain source and support for discovering and investigating definitive therapies, the goal of this act was to introduce incentive programs to develop new drugs and treatment strategies for rare or orphan diseases.[4]

Overall, 6 to 8% of population globally has been estimated to be affected by rare diseases that include wide array of autoimmune disorders, tropical infectious diseases, genetic disorders, and cancer subtypes. Rare diseases have been found to affect small fewer than 100 patients per 100,000 population; around 250 new rare diseases are discovered each year across the globe; and another category of rare diseases termed as "ultrarare" diseases has been estimated to affect 2 patients per 100,000 population. European Commission has revealed that in European Union there are 6,000 distinct rare diseases and up to 36 million people live with a rare disease.[5] Rare diseases are more prevalent in South Asian countries and have been reported to exhibit geographical variations, but there is lack of clear evidence. Hence, in future exploring such variations could contribute to new dimensions in the field of medicine.[6]

As per literature, 80% of orphan diseases are chronic, serious or life threatening, are of genetic origin, and are more prevalent in children and in adults above 40 years of age.[2] Due to rarity, lack of financial support, and specific drug to treat these disorders, diagnosis and treatment become challenging, due to which diagnosis is delayed, and patient continues to suffer by seeking multiple consultations. Another barrier is nonavailability of specific drug or uncertainty of therapeutic intervention; moreover, pharmaceutical companies raise the cost of manufactured drug that is beyond the affordability of patient and researcher to conduct clinical trial.[4,5] Hence, there is a need for policy measures in recognition of orphan diseases to formulate comprehensive holistic approach to tackle them and to encourage pharmaceutical companies for invention of drugs at a reasonable cost for orphan diseases. To this consideration, this review aims to discuss challenges faced by patients particularly children with orphan diseases and by the specialists toward diagnosis and treatment of an orphan disease for well-being of an individual living with the disorder.

## Etiology and Pathogenesis

Orphan diseases can be heritable or inheritable, and 80% of these disorders have been reported to be heritable or genetic in origin with chromosomal or genetic abnormality as a causative factor.[1,2] Few reports have revealed that some social or cultural factors may play a role in the development of an orphan disease in a particular community and tradition of consanguineous marriage is a major cause of higher incidence of autosomal recessive conditions, congenital malformations, stillbirths, and mental retardation in the offspring.[7] In few instances, environmental factors such as diet, smoking, and exposure to chemicals can interact with genetic factors to cause or increase the severity of the disease.[7]

Chemical genetics has provided a new horizon to understand the molecular and cellular mechanisms associated with neurological illnesses such as amyotrophic lateral sclerosis (ALS), Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), and familial amyloid polyneuropathy (FAP) that include glutamate excitotoxicity, oxidative stress, mitochondrial dysfunction, and neuroinflammation. Understanding of these mechanisms could help in the development of targeted drugs for the specific orphan disease.[8]

## Clinical Features of Orphan Diseases

Clinical features of an orphan disease may vary from disease to disease, and even there are different subtypes of same disease. These diseases affect physical and mental behavior and cognitive abilities of an individual, and many disabilities may coexist in a same patient; hence, they are described as "polyhandicap."[9] In addition, there is diversity observed in the age at which symptoms first occur. Symptoms of orphan diseases such as osteogenesis imperfecta and chondrodysplasia may appear at the time of birth or in childhood.[9,10] Symptoms in child may resemble posttraumatic stress disorder such as depression, fear anxiety, and limited ability to react to untoward situations in a positive way. In adults, childhood traumatic experiences could result in wide array of chronic illnesses such as cancer, cardiac and liver diseases, diabetes mellitus, and autoimmune diseases. Other physical symptoms include eating disorders, obesity, and sleep disturbances. They may be at an increased risk of developing mental and personality disorders, and could have difficulty in maintaining interpersonal relationships.[9,10]

## Orphan Disease as a Public Health Concern

Discovery of definitive treatment of orphan diseases has become a public health concern. The WHO report on Priority Medicines for Europe and the World published on October 7, 2004 has revealed that epidemiological data available is insufficient to provide information of patients with specific

orphan disease.[1,7] Another issue is that patients with orphan diseases are not registered on databases, and due to systemic manifestations majority of patients are grouped under endocrine or metabolic disorders, and it becomes difficult to register people with a rare or an orphan disease on national and international databases. Genetic disorders are also considered as orphan diseases; however, these may have no severe consequences. On the other hand, if two individuals are diagnosed with same genetic or chromosomal abnormality, the genes may get transferred to the children.[11] It is important to understand the characteristics of orphan diseases that include (i) around 50% diseases occur in children, and nearly all have genetic abnormality as a causative factor; (ii) correct diagnosis of orphan diseases is a challenge, and may be undiagnosed for several years; (iii) majority of the orphan diseases have been proven to have multisystem manifestations as a result they are not sufficiently investigated and proper reliable diagnosis is not achieved; and (iv) for majority of diseases, in 95% of cases there are no definitive therapies.[1,2]

It has been established by epidemiological surveys that orphan diseases are rarely encountered; hence, there is incorrect interpretation of the symptoms by the specialists, patients, and the family members. Patient and his/her family member suffer from psychological distress, and are in fear about the progression and outcome of the disease. In these scenarios, specialists who intend to offer psychosocial and supportive care are a great source of support to the patients and their family. However, the major obstacle is lack of access to healthcare facilities and specialists as the patients are often dependent on few specialists. Other contributing factors are inadequate awareness of the patients about required expertise and specific specialists or healthcare centers that may be difficult to find due to spatial distance.

## Diagnosis of Orphan Diseases

Orphan diseases have been documented to be caused by defects in single- and double-stranded DNA break repair mechanisms, as a result genetic testing, such as exome sequencing and whole genome sequencing, has become an important diagnostic tool for the detection of genes implicated in the development of an orphan disease. Genetic counseling has a key role to play in diagnosis and sustainability of quality of life of patients living with the rare condition. It can help to select the suitable DNA test and to understand the genetic report.[12,13] Currently, DNA-powered apps have been introduced to analyze the raw DNA data from a wide range of genetic tests and genome sequences. DNA apps with home saliva collection kits are available by which parents can explore their future child genetic characteristics such as color of hair and eyes based on the results of the DNA apps.[14] Recently, chemical genetics is becoming popular to elucidate the underlying molecular mechanism toward the development of neurological illnesses like ALS, DMD, SMA, and FAP that are rarely reported and to investigate how the small molecules can be used to study genetic basis for the treatment of an orphan or rare disease.[11]

## Dental-Craniofacial Manifestations of Orphan Diseases

Orphan diseases usually have dental-craniofacial manifestations; however, due to low prevalence, these disorders are not thoroughly understood and patients incur delay in diagnosis and treatment. Most of the orphan diseases have genetic abnormality, and different stages of bone development are affected by the heritable changes that in turn affect the development and formation of bones and teeth.[9] Particular disease can affect specific stage of bone formation and remodeling contributing toward various dental craniofacial manifestations as (i) defective stem/progenitor cell differentiation in McCune-Albright syndrome characterized by triad of polyostotic fibrous dysplasia of bone, Caif-au-lait skin pigmentation, and precocious puberty; (ii) defective matrix formation in osteogenesis imperfecta, (iii) defective matrix mineralization in hyperostosis hyperphosphatemia syndrome and hypophosphatemic rickets, (iv) bone resorption in Gorham-Stout disease characterized by massive osteolysis due to enhanced osteoclastic activity.[9] ►**Table 1** illustrates various dental craniofacial manifestations related to an orphan diseases.

## Management Strategies for Orphan Diseases

Diagnosis and treatment of the patients presenting with dental craniofacial manifestations are a challenge for clinicians, and in most of the instances, proper diagnosis is delayed for years that adversely impacts the quality of life of patients.

- First, psychosocial, emotional, and spiritual concerns should be addressed in these patients, as both patient and his/her family member may be under psychological distress due to disease or because of multiple consultations without any beneficial outcome. Although orphanage homes are available to provide shelter to the children living with the disorder, as these children are often abandoned by family; however, to address the special needs, they require special healthcare centers and specialists. Spiritual beliefs should also be paid attention as patients and his /her family may develop firm faith in God during the course of disease and resort to frequent religious visits as they believe the disease to be part of their past Karma.[15]
- The control of genetic diseases requires comprehensive integrative approach through community education, population screening, and genetic counseling for early diagnosis. Therefore, physicians should have effective communication skills during an interaction with the patient and caregiver, and should take time to talk and listen to the presenting dental problem in a friendly manner.[7,16]
- Majority of orphan diseases are of genetic origin; therefore, education in genetics is need of an hour. Education sessions should be conducted at both an individual and population level; people should be made aware of the

**Table 1** Dental craniofacial manifestations of teeth- and bone-related orphan or rare diseases

| Orphan or rare disease | Etiology | Onset period | Major manifestations | Dental craniofacial manifestations |
|---|---|---|---|---|
| Hypohidrotic ectodermal dysplasia | Abnormalities of the ectodermal structures, X-linked inheritance pattern with the gene mapping to Xq12-q13 | Childhood | Skin appears lightly pigmented, fine sparse hair, reduced density of eyebrow and eyelash hair, dry fragile hair, thick brittle discolored nails, poorly developed or absent salivary glands and sweat glands, brown hyperpigmentation on skin | Hypodontia, peg-shaped teeth, taurodontism, enamel hypoplasia, reduced salivary secretion |
| Williams syndrome | Autosomal dominant condition, genetic deletion of chromosome 7q11.23 | Early childhood | Mild or moderate intellectual disability, short stature, distinctive facial features that include broad forehead; a short nose with a broad tip; full cheeks; and a wide mouth with full lips, unique personality with high levels of anxiety and exhibit attention deficit disorder, cardiovascular defects such as supravalvular aortic stenosis | Small jaw, malocclusion with widely spaced teeth, hypodontia, enamel hypoplasia, taurodontism, pulp stones |
| Osteogenesis imperfecta | Autosomal dominant inheritance, may have autosomal recessive inheritance with mutations in the COL1A1 or COL1A2 genes, CRTAP, LEPRE 1 gene | Childhood or adulthood | Brittle and fragile bones, bowing of legs, blue or gray sclera, barrel shaped chest, curved spine, hearing loss | Skeletal class III malocclusion, open bite, impacted teeth, dentinogenesis imperfecta |
| Hypophosphatemic rickets | X-linked dominant, mutations in the phosphate regulating endopeptidase (PHEX) gene | At birth or early childhood | Bowing of legs, bone pain, joint pain, poor bone growth, short stature | Premature loss of deciduous teeth, delayed tooth eruption, taurodontism, decrease in height of alveolar bone, malocclusion |
| Marfan syndrome | Mutations in the gene FBN1, encoding fibrillin, a major component of microfibrils | Childhood | Tall stature, joint hypermobility, ligamentous laxity, disproportionately long slender legs, disproportionate long fingers and toes (arachnodactyly) dolichocephaly, high palate, scoliosis, cold arms, hands and feet, aortic regurgitation | Long narrow skull, high arched palate, localized enamel hypoplasia, root deformity, abnormal pulp shape, maxillary and mandibular retrognathy, dental crowding, supernumerary teeth |
| McCune-Albright syndrome | Mutations in GNAS 1 gene | At birth, early childhood and childhood | Triad consisting of polyostotic fibrous dysplasia of bone, Café -au-lait skin pigmentation, and precocious puberty | Facial asymmetry, oral mucosal pigmentation, dental malocclusion, dentin dysplasia, taurodontism |

possible etiological factors and the need to consult specific specialists and healthcare centers. Countries should formulate health polices to increase awareness and provide education to communities about genetics, and this could be accomplished by incorporation of modules on genetic counseling. Whenever rare skeletal disease is recognized, it is important to refer such patients to craniofacial team for thorough clinical evaluation for early diagnosis.[9]

- Intervention programs comprising of behavioral education and genetic counseling should be performed for children with developmental and intellectual disabilities and they should be explained about the role of genetics, and the need to visit the specialist. The major barrier to accomplish these programs for adequate control of a rare or an orphan disease is lack of adequate access to specialized healthcare centers, and most of the patients are fearful to consult specialists. Children should be managed by comprehensive supportive care taking into consideration psychosocial, behavioral, ethical, and spiritual issues that may arise while counseling or at the time of diagnosis and it is recommended to refer children with dento-cranio-facial and skeletal abnormalities with intellectual disability to special care specialists for optimal quality of life.
- Consideration of an ethical, legal, and social issues associated with orphan diseases of genetic origin should be an integral part of genetic education and healthcare workers should ensure the patient about the confidentiality of his/her genetic information. Currently, the WHO has taken an initiative to work in collaboration with nongovernmental organizations with a goal to support and implement genetic approaches to control heritable orphan diseases in various countries.[10,11]
- Literature has also revealed level of poverty, and malnutrition as the major risk factors for increase in morbidity due to rare and orphan diseases in developing countries.[1,2] Another obstacle is the introduction of new specific drugs to treat orphan or rare disease due to lack of financial resources and high cost of drug development. Despite continuous progression in medical science, in developing countries many patients cannot afford the newly developed generic drugs or new technologies to investigate their condition. According to Orphan Drug Act of 1983, drug to treat or prevent a rare disease is not expected to recover development and marketing costs. Hence, pharmaceutical companies assume that cost of production of an orphan drug and its availability in the market could not be recovered by expected sales. For drug development, measures such as financial incentives comprising research and clinical trials grants and extended market exclusivity, that is, for an orphan drug around 7 years should be undertaken and risk–benefit ratio of new generic drug should be individually assessed.[17,18]
- Drug toxicity and safety should be taken into account for patient's well-being and survival. Health policies and measures for access to health resources for better patient outcome should be designed and implemented.[18]

## Conclusion

Orphan diseases affect physical and mental behavior and cognitive abilities of an individual. Comprehensive integrative approach should be practiced while attending special care patients, and this can be accomplished by the use of effective communication skills, addressing patients' needs, and providing them psychosocial support. In addition, community education, population screening, and genetic counseling are necessary to increase awareness of population particularly in developing countries about the orphan or rare diseases. Health policies should be implemented and financial incentives should be provided to pharmaceutical companies for the development of new orphan drug taking into consideration risk–benefit ratio of drug, drug toxicity, and safety for patient well-being and better outcome.

Conflict of Interest
None declared.

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