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


Sarita Singh, Manju Pandey*
Institute of Pharmacy of Shri Ramswaroop Memorial University, Barabanki, Uttar Pradesh -225003
Email: manju16824@gmail.com

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

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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.

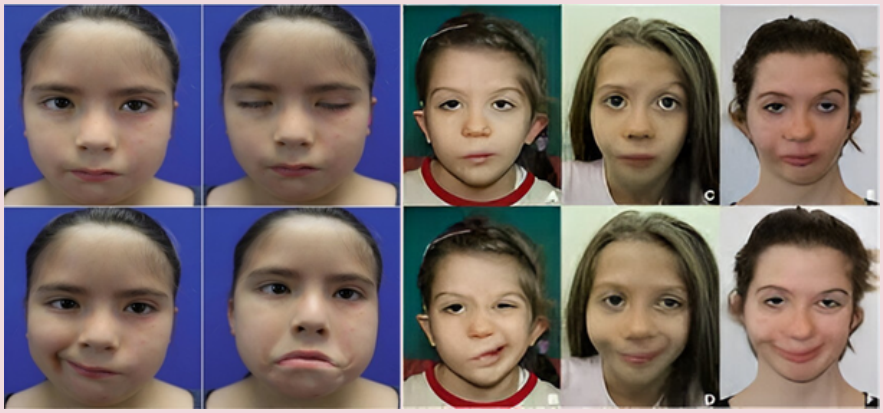

Figure 1. Facial changes due to Mobius syndrome in individuals (Source: https://samarpanphysioclinic.com/moebius-syndrome)

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.

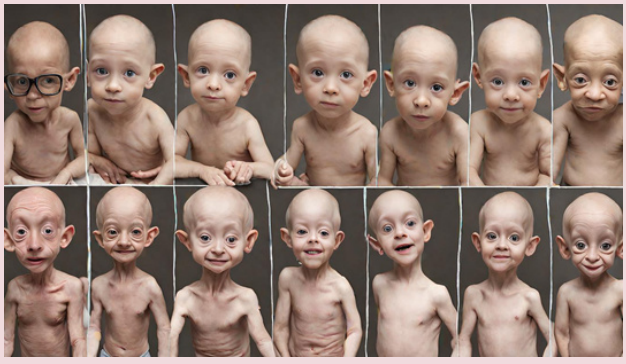

Figure 2. Disease the progression of Progeria from childhood till later age (Figure source: AI generated)

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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