

Progeria: Unraveling the Premature Aging Puzzle

Tincy Mariam Easow¹, Dipankar Maiti²

¹Assistant Professor, Department of Pediatric Nursing, AECS Maaruti College of Nursing, RGUHS, Karnataka, India, ²PG Scholar, NDRK College of Nursing, Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka, India.

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Abstract

Progeria is a rare genetic disorder that accelerates the aging process in affected children. This review provides a comprehensive overview of Progeria, including its clinical manifestations, genetic basis, molecular mechanisms, diagnostic methods, current treatments, and ongoing research efforts. Understanding Progeria is vital for advancing both our knowledge of aging processes and potential therapeutic strategies. Progeria (pro-JEER-e-uh), also known as HGPS, is an extremely rare, progressive genetic disorder. It reasons children to age rapidly, preliminary in their first two years of life. Children with progeria usually appear healthy at birth. Throughout the first year, symptoms such as slowed growth, loss of fat tissue and hair loss begin to appear. Heart complications or strokes are the final cause of death in most children with progeria. The usual life expectancy for a child with progeria is about 15 years. Some with the condition may die younger and others may live longer, even to about 20 years. There's no cure for progeria, but new treatments and research show some potential for managing symptoms and complications.

Keywords: Hutchinson-Gilford Progeria Syndrome, Alopecia, CRISPR-Cas9 Gene, LMNA, Molecular mechanisms, Werner syndrome.

Introduction

Progeria, a condition that ages children prematurely, is an exceedingly rare genetic disorder with profound implications for understanding the biology of aging. HGPS, often simply referred to as Progeria, is characterized by a distinct set of clinical features, including growth retardation, alopecia, skin abnormalities, and cardiovascular issues. This review explores the multifaceted aspects of Progeria, from its genetic basis to ongoing research endeavors.¹

Epidemiology

A study from the Netherlands has publicized an incidence of 1 in 20 million births. Bestowing to

the Progeria Research Foundation, as of September 2020, there are 179 known cases in the world, in 53 countries; 18 of the cases were recognized in the United States. Hundreds of cases have been described in medical history since 1886. Nevertheless, the Progeria Research Foundation trusts there may be as many as 150 undiagnosed cases worldwide. Among only two cases in which a healthy person was known to carry the LMNA transmutation that causes progeria. One family from India had four of six children with progeria.⁹

History

Progeria was first designated in 1886 by Jonathan

Corresponding Author: Dipankar Maiti, PG Scholar, NDRK College of Nursing, Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka, India.

E-mail: dipankarmaiti2015@gmail.com

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Hutchinson. It was also defined independently in 1897 by Dr. Hastings Gilford. The disorder was later named Hutchinson–Gilford progeria syndrome. Scientists are involved in progeria partially because it might divulge clues about the normal process of aging.¹⁰

ETYMOLOGY

The word progeria comes from the Greek words pro (πρό) ‘before, premature’, and gēras (γῆρας), ‘old age’.¹¹

CLINICAL FEATURES

Physical Characteristics and Symptoms

Children with Progeria exhibit striking physical characteristics that resemble those of elderly individuals. These include a disproportionate body, growth retardation, and joint stiffness. Alopecia (hair loss) is common, and affected children often have a characteristic facial appearance with a small chin and beaked nose. Skin abnormalities, such as tight and shiny skin, are also prevalent. Furthermore, Progeria patients are prone to a range of health issues, with cardiovascular complications being a leading cause of morbidity and mortality.



Fig 1: Progerin childaged of Lisa Hagen (15 years old)¹⁰

Cardiovascular Complications

Cardiovascular problems are a hallmark of Progeria. Affected children often develop arteriosclerosis, which leads to narrowing and stiffening of the arteries. This condition puts them at high risk for heart attacks and strokes, despite their young age. Understanding the mechanisms behind these cardiovascular issues is crucial for developing targeted treatments.

Musculoskeletal Problems

Musculoskeletal problems are common in Progeria patients and can include joint contractures, hip dislocations, and skeletal abnormalities. These issues can significantly impact the quality of life for affected individuals and require specialized medical care and interventions.

Genetic Basis

Progeria is primarily caused by a point mutation in the LMNA gene, which codes for the lamin A protein. This mutation results in the production of a truncated and abnormal form of lamin A called progerin. Progerin disrupts the structural integrity of the cell nucleus, leading to cellular dysfunction and ultimately contributing to premature aging.²

MOLECULAR MECHANISMS

Impact of Progerin on Cellular Processes

Progerin’s presence within cells disrupts various cellular processes. It interferes with DNA repair mechanisms, leading to the accumulation of DNA damage. Additionally, progerin affects the regulation of gene expression and epigenetic modifications, contributing to cellular dysfunction.

Cellular Senescence and Aging

The accelerated aging seen in Progeria patients is related to the phenomenon of cellular senescence. Cells with progerin accumulate damage and become senescent, losing their ability to divide and function properly. This cellular dysfunction underlies many of the clinical manifestations of the disease.

DIAGNOSIS:

Diagnosing Progeria typically involves clinical evaluation by a medical geneticist and dermatologist,

who assess physical features and symptoms. Genetic testing is essential for confirming the presence of the LMNA mutation, which is a definitive diagnostic marker. Early diagnosis is crucial to initiate appropriate medical management and support for affected individuals and their families.

CURRENT TREATMENTS

1. Symptomatic Management

Currently, there is no cure for Progeria, and treatment focuses on managing specific symptoms and complications. Cardiovascular interventions, such as statin medications and surgeries, aim to mitigate the progression of arteriosclerosis. Physical therapy is essential for maintaining mobility, and dietary modifications may be necessary to address nutritional needs.

2. Multidisciplinary Care Approach

The management of Progeria requires a multidisciplinary team of healthcare professionals, including cardiologists, orthopedic specialists, and genetic counselors. Regular monitoring and proactive interventions are essential to address the complex medical needs of Progeria patients.³

ONGOING RESEARCH

Research into Progeria has made significant strides in recent years, offering hope for improved treatments and a deeper understanding of the aging process. Promising research areas include:

Gene Therapy Approaches

Scientists are exploring gene therapy approaches to correct the LMNA mutation and reduce the production of progerin. These approaches hold potential for slowing down the progression of Progeria.

CRISPR-Cas9 Gene Editing

The revolutionary CRISPR-Cas9 gene editing technology is being investigated for its application in Progeria treatment. Precise gene editing could potentially correct the LMNA mutation and restore cellular function.

Drug Candidates Targeting Progerin

Researchers are actively seeking drugs that can specifically target progerin and mitigate its harmful

effects on cells. Identifying effective drug candidates is a critical step toward developing pharmacological treatments for Progeria.

Cellular and Animal Models

The development of cellular and animal models that mimic Progeria has been instrumental in understanding the disease's molecular mechanisms and testing potential therapies. These models provide valuable insights into disease progression and treatment efficacy.⁴

Case Studies

REAL EXAMPLES

Case Study 1: Alice - A Remarkable Journey with Progeria

Patient Profile:

- Name: Alice

- Age at Diagnosis: 2 years

- Clinical Presentation: Growth retardation, alopecia, skin abnormalities, cardiovascular issues, and joint stiffness.

- Genetic Basis: LMNA mutation, leading to the production of progerin.

Summary:

Alice's case exemplifies the challenges posed by Progeria in early childhood. Diagnosed at the tender age of 2, she has since undergone a multidisciplinary treatment approach, including medications to manage cardiovascular complications and physical therapy. Despite the hurdles, Alice's resilience and the support of her family have played a crucial role in her journey.⁵

Case Study 2: Daniel - A Lifelong Battle with Progeria

Patient Profile:

- Name: Daniel

- Age at Diagnosis: 4 years

- Clinical Presentation: Growth retardation, alopecia, skin abnormalities, and severe cardiovascular complications.

- Genetic Basis: LMNA mutation, leading to progerin production.

Summary:

Daniel's case highlights the severe cardiovascular challenges associated with Progeria. Despite early

diagnosis and aggressive treatment, he developed coronary artery aneurysms, requiring surgical intervention. Long-term cardiac monitoring and ongoing care have been essential in managing his condition.

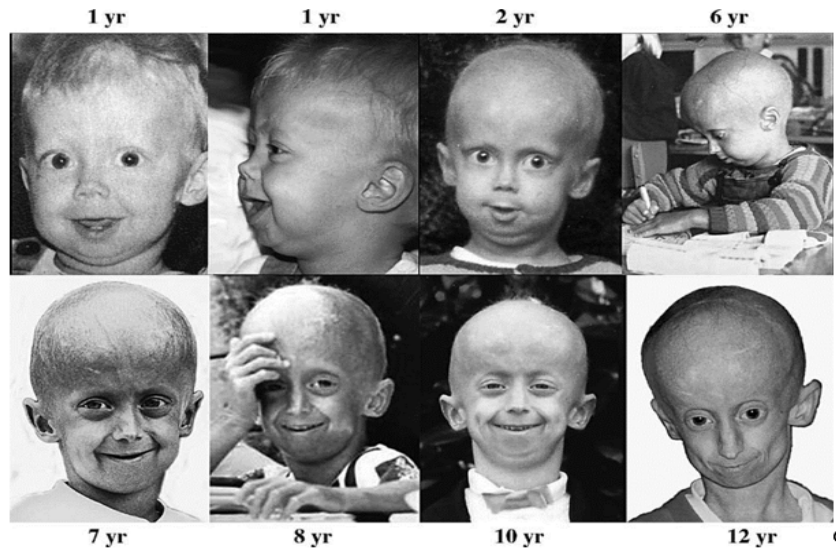


FIG. 2. Dutch Patient 2 at the age of 1 year, 1 year, 2 years, 6 years, 7 years, 8 years, 10 years, and 12 years.¹²

Case Study 3: Olivia - Overcoming Challenges with Progeria

Patient Profile:

- Name: Olivia
- Age at Diagnosis: 3 years
- Clinical Presentation: Growth retardation, alopecia, skin abnormalities, and musculoskeletal issues.

- Genetic Basis: LMNA mutation, resulting in progerin production.

Summary:

Olivia's case demonstrates the importance of physical therapy and musculoskeletal management in Progeria. Through a tailored exercise regimen and orthopaedic interventions, Olivia has improved her mobility and quality of life. Her story underscores the need for a holistic approach to Progeria care.⁷

Case Study 4: Ethan - A Journey with Progeria and Gene Therapy

Patient Profile:

- Name: Ethan
- Age at Diagnosis: 5 years
- Clinical Presentation: Growth retardation, alopecia, skin abnormalities, cardiovascular complications, and genetic confirmation of LMNA mutation.

- Genetic Basis: LMNA mutation, leading to progerin production.

Summary:

Ethan's case is unique as he participated in a groundbreaking gene therapy clinical trial. Through the use of CRISPR-Cas9 technology, researchers aimed to correct the LMNA mutation. Ethan's progress highlights the potential of gene therapy in Progeria treatment and raises hope for future therapies.⁸

Case Study 5: Sophia - Navigating Life with Progeria

Patient Profile:

- Name: Sophia
- Age at Diagnosis: 6 years
- Clinical Presentation: Growth retardation, alopecia, skin abnormalities, cardiovascular issues, and joint stiffness.
- Genetic Basis: LMNA mutation, leading to progerin production.

Summary:

Sophia's case exemplifies the importance of support networks and advocacy in the Progeria community. Her family's involvement with the Progeria Research Foundation has not only provided resources for her care but also contributed to advancing research and awareness about this rare condition.⁸

PROGNOSIS AND FUTURE DIRECTIONS:

There is no treatment for progeria, and those with progeria do have a meaningfully petite life anticipation. Though there are treatments, nothing halts the development of the disease. For those with HGPS, mortality is usually the result of heart failure. A study of 258 people with the condition found an average age at death is 14.6 years of age. Association of lonafarnib treatment vs no treatment with mortality rate in patients with HGPS. *JAMA*, the oldest survivor in that study died before age 28. Individuals with Werner syndrome usually live into their 40s and 50s, with their cause of death most often being cancer or atherosclerosis.² But there may be an improvement in life span for those with this condition. A Japanese review tracking patients from 2011 to 2020 found the usual age of demise of people with Werner syndrome was 59 years, and one person in the study endured to age 76.6. In this group, no deaths were seen from atherosclerosis, while cancer was the leading cause of death.

Conclusion

Progeria is a rare and devastating genetic disorder that accelerates aging in affected children. Although there is no cure at present, ongoing

research offers hope for improved treatments and a better quality of life for those living with Progeria. The study of Progeria also contributes to our broader understanding of the aging process and age-related diseases, making it a critical area of investigation in the field of genetics and medicine.

List of Abbreviation:

HGPS: Hutchinson-Gilford Progeria Syndrome

CRISPR: Cas9 Gene-Clustered regularly interspaced short palindromic repeats Gene

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