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HUTCHINSON GILFORD PROGERIA SYNDROME - A REVIEW

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ABSTRACT

Hutchinson-Gilford Progeria Syndrome is a very rare disorder characterized by premature aging caused by a mutation in the LMNA gene. The child born with this disorder shows features of old age from the first year of birth and generally dies in the teenage. The clinical symptoms include alopecia, thin skin, stiffness of joints, etc. All of the children suffering from this disease appear identical. The pathophysiology of the disease is not very clearly understood. Various methods for diagnosis are being developed and clinical trials on some drugs that may be used in treatment are being carried out. The aim of this review is to understand the various aspects of the disease with special emphasis on pathophysiology, symptoms, recent trends in treatment, and future opportunities.

KEYWORDS: The pathophysiology of the disease is not very clearly understood.

INTRODUCTION

Hutchinson Gilford Progeria Syndrome is a rare, sporadic, autosomal dominant, fatal childhood disease first described by Dr Jonathan Hutchinson in 1886. Dr. Hastings Gilford reported similar clinical findings and named the condition as Program. The term Progeria is derived from the Greek word geras, meaning old age, and Latin meaning Progeria is being

prematurely old. The disease involves premature aging, generally leading to death due to myocardial infarction or stroke.

The disorder has a very low incidence and occurs in one per four million live births. Those born with Progeria typically live about thirteen years, although many have been known to live into their late teens and early twenties. Very rare individuals may even reach their forties.[2]

It is a genetic condition that occurs as a new mutation in one gene and is not usually inherited, although there is a uniquely inheritable form. The aging process of the body accelerates much faster than it does in normal humans.

A study that compared HGPS patient cells with the skin cells from LMNA young and elderly human subjects found similar defects in the HGPS and elderly cells, including down-regulation of certain nuclear proteins, increased DNA damage, and demethylation of histone, leading to reduced heterochromatin. Children with Progeria appear normal at birth while the symptoms manifest in the first or second year of life when skin changes, failure to gain weight, alopecia, etc.

In 2003, a group of French researchers discovered point mutations in the LMNA genes. Progeria, a laminopathy, was caused by the mutation of Lamin A which, encoded by the LMNAintact. However, when Lamin A undergoes mutation, it causes destabilization of the nuclei.[9]

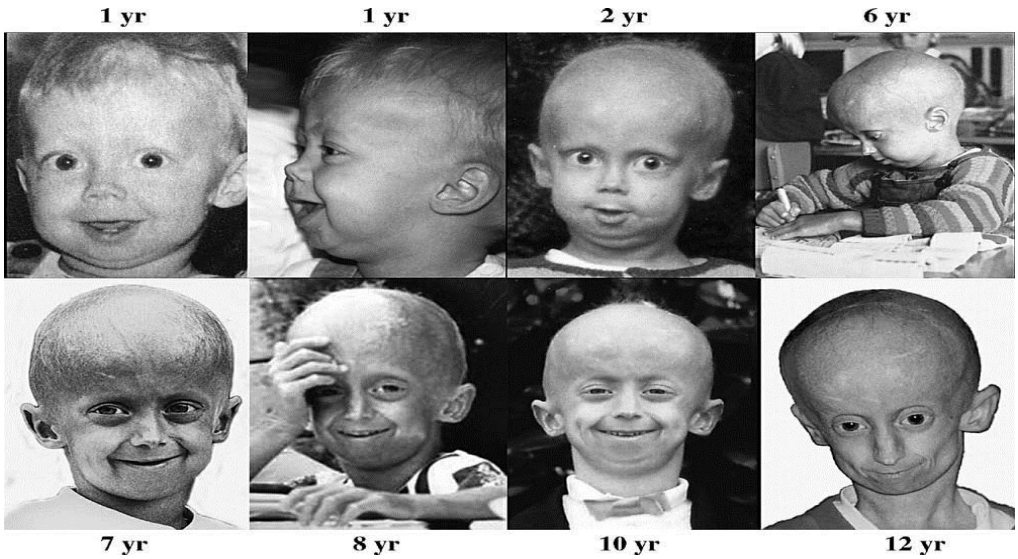

Fig 1: Hutchinson Gilford progeria syndrome.

HISTORY

Progeria was first described in 1886 by Jonathan Hutchinson. It was also described independently in 1897 by Hasting Gilford. The condition was later named Hutchinson–Gilford progeria syndrome.

It affects 1 in 20 million people. Lonafarnib was approved for the first time in the United States in November 2020 to reduce the risk of mortality in HGPS and treat processing deficient progeroid laminopathies.[1]

SIGH AND SYMPTOMS

Usually, within the first year of life, you'll notice that your child's growth has slowed. However, motor development and intelligence are not affected.

Symptoms of this progressive disorder cause a distinctive appearance. They include.

- Slowed growth and poor weight gain, with below-average height and weight.
- Lack of fat that's stored just beneath the skin.
- Head that is large compared with the face.
- Small jaw, chin, and mouth and thin lips
- Thin, curved nose with a slight hook at the end, which may look like a bird's beak.
- Large eyes and eyelids that don't close completely.
- Hair loss, including eyelashes and eyebrows, Thin, spotty, and wrinkled skin.
- Veins easily seen through the skin.
- High-pitched voice.
- Premature aging.

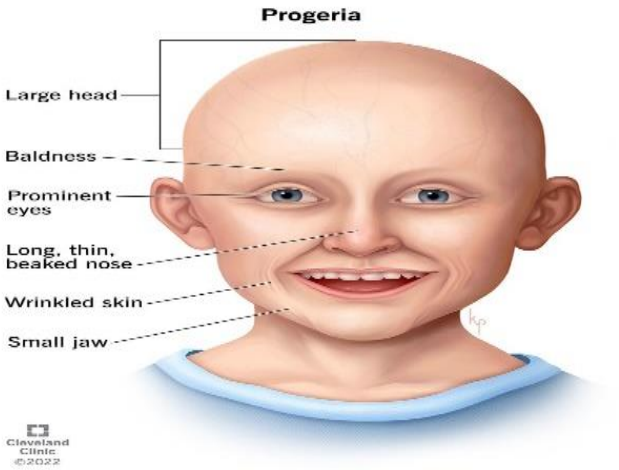

Fig. 2: Signs And Symptoms.

CAUSES

A change in one gene causes progeria. This gene, known as Lamin A (LMNA), makes a protein that's needed to hold the center of a cell, called the nucleus, together. When the LMNA gene has a change, a flawed Lamin A protein called progerin is made. Progeria makes cells unstable and appears to lead to progeria's aging process.[8]

The changed gene that causes progeria is rarely passed down in families. In most cases, the rare gene change that causes progeria happens by chance.

RISK FACTORS

There are no known factors, such as lifestyle or environmental issues, that increase the risk of having progeria or giving birth to a child with progeria. However, the age of the father has been described as a possible risk factor. Progeria is extremely rare. If you've had one child with progeria, the chances of having a second child with progeria are slightly higher than the general population but are still low. If you have a child with progeria, a genetic counselor can give you information about the risk of having other children with progeria.[3]

PATHOPHYSIOLOGY

The major symptoms in the patient with HGPS occur due to a mutation in the gene LMNA. The gene, LMNA, located on band 1q21.1-1q21.3, encodes Lamin A, which is a type V intermediate filament protein that localizes to the cell nucleus and forms the nuclear lamina inside the nuclear membrane. De novo mutations associated with advanced paternal age are responsible for most cases. Lamin A and Lamin C, two abundant structural proteins of the nuclear lamina, are products of the same gene, LMNA. Lamin A is an exon protein. Prelamin A, the precursor of Lamin A, involves the splicing from the middle of exon 10 to exon 11 and then to exon. Prelamin A has CAAX as a terminal amino acid.

This terminal triggers farnesyl Tion of the carboxy-terminal cysteine (the C of the CAAX tetrapeptide) by a cytosolic enzyme, known as protein farnesyltransferase. The farnesylated Prelamin A attaches to the Endoplasmic Reticulum. After farnesyl Tion, the last three amino acids of Prelamin A are cleaved by an Endo protease. The enzymes responsible for the release of these amino acids are a Zinc metalloprotein ZMPSTE24 and a phenyl protein endopeptidase RCE1. After the release of the terminal amino acids, the farnesyl-cysteine residue is methylated by an enzyme Isoprenylcystein Carboxy Methyl Transferase (ICMT). In the last step of normal Lamin, A synthesis, the end 15 amino acids of Prelamin A

including farnesylcystein methyl ester are released off by ZMPSTE24 and mature Lamin A is released from the endoplasmic reticulum into cytosol. The resulting protein, now Lamin A, is no longer membrane-bound and carries out functions inside the nucleus.[4]

In the diseased person, there is a mutation in one allele of the LMNA gene. Approximately 90% of patients with the syndrome have an identical mutation in one allele of the gene, consisting of a C-to-T substitution at nucleotide 1824 (1824 C→T) 24. The disorder is rare because affected people die before reproductive age, so every case represents a new mutation, and the mutation needs to be precisely targeted to produce the phenotype. The LMNA mutation at position 1824 does not change the amino acid of the corresponding codon in the messenger RNA (mRNA). But it causes defective mRNA splicing by activating a cryptic splice donor in exon 11, resulting in a synthesis of an abnormal protein named "Progerin," with an internal deficiency of 150 bases i.e., 50 amino acids as compared with normal Lamin A. The defective splicing caused by the 1824 CT mutation deletes the part of the protein that is targeted by ZMPSTE24 at the release step.[10]

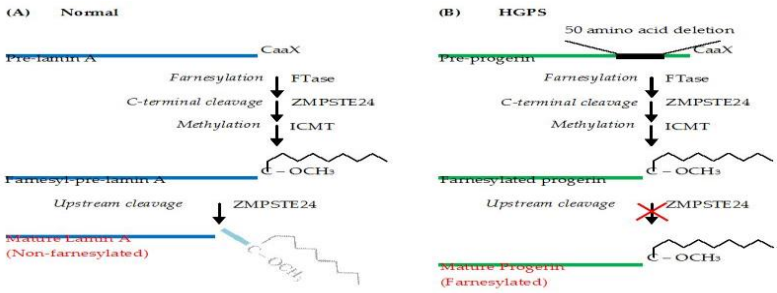

Fig. 3: Pathophysiology of Hutchinson Gilford progeria syndrome.

CLINICAL MANIFESTATIONS

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 characteristics of the Program. The characteristic clinical findings of Hutchinson-Gilford Progeria syndrome (HGPS) include abnormalities of the skin and hair in addition to characteristic facial features and skeletal abnormalities. Delayed, abnormal dentition is also common. 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.[6]

Skin and hair: Skin changes at the time of birth may be present. The major abnormalities include shiny and elastic skin. The skin may appear wrinkled with low cutaneous fat. The patient is physically weak. When in contact with bright sunlight, hyperpigmentation of the skin may occur with irritation. Complete loss of hair of all the body parts including the scalp, eyelashes, and skin.

Musculoskeletal abnormalities: The limbs are thin with low muscular mass. The joints appear prominent. There may be flexion of the knee joint leading to disturbed gait. The patient walks a bit abnormally. The thoracic cage becomes pear-shaped. The face appears like an aged person, with prominent eyes and ears slightly bigger in size. In scissors fall at an early age. Other reported abnormalities: The voice has a high pitch. Scars may be present over the body. Weight to height ratio is low. The nails may appear dystrophic. The patient generally suffers from hypertension. Difficulty in hearing or even complete loss may accompany. Osteoporosis is a major feature of weak bones. The patient is prone to fractures. There may be a complete loss of appetite. Delayed teeth growth or loss of teeth is a prominent clinical feature. The prothrombin time is prolonged with elevated platelet count. The serum level of phosphorus increases and that of calcium decreases. Emotionally, patients with HGPS have feelings similar to that of age-matched healthy persons. They express proper mood and affection.

DIAGNOSIS

The diagnosis of the disease depends upon the proper interpretation of clinical and radiological findings. The characteristic radiological findings include abnormalities in the skull, thoracic cage, long bones, and phalanges. Acro osteolysis is the earliest abnormal finding, and joint contracture preceded the development of coxa valga. The cranial bones tend to be hypoplastic and fontanels become open and longer than expected. The presence of Wormian bones is common. Narrowing of posterior ribs is frequent with thinning of distal clavicles. The loss of bones of fingers and toes are major abnormality associated with the progression of the disease. Elevated levels of hyaluronic acid are seen in urine. Brain magnetic resonance angiography may identify cerebrovascular occlusive disease. ECG and echocardiography should be performed to monitor coronary artery disease and congestive heart failure.[5]

Healthcare providers may suspect progeria based on symptoms. A genetic test for changes in the LMNA gene can confirm the diagnosis of progeria.

A thorough physical exam of your child includes.

- Measuring height and weight.
- Putting measurements on a growth curve chart.
- Testing hearing and vision.
- Measuring vital signs, including blood pressure.
- Looking for visible symptoms of progeria.

Progeria is a very rare condition. healthcare provider may need to gather more information before deciding on the next steps in caring for children.

TREATMENT AND MANAGEMENT

There's no cure for progeria. However regular monitoring for heart and blood vessel disease may help with managing your child's condition. child's weight and height are measured and put on a chart that shows average measurements of children's age. Routine evaluations often include electrocardiograms and echocardiograms to check the heart, imaging tests, such as X-ray and MRI, and dental, vision, and hearing.[7]

Certain therapies may ease or delay some of the symptoms of progeria. Treatments depend on the child's condition and symptoms. These may include.

- Other medications: Depending on the child`s condition, the doctor may prescribe other medications. e.g. anticoagulants to help prevent blood clots.
- The growth hormone may help increase height and weight.
- Physical and occupational therapy. These may help with joint stiffness and hip problems and may allow the child to remain active.
- Extraction of primary teeth: Extraction may help prevent problems associated with the delayed loss of baby teeth.
- **Ophthalmologic.** Corneal dryness, clouding, or ulceration should be fully evaluated by an ophthalmologist. Exposure keratitis can be treated during daytime with ocular lubrication and during sleep with moisturizing ointment or by closing eyelids with skin tape.
- **Hearing loss**. Low-frequency conductive hearing loss often does not interfere with activities of daily living. Sitting at the front of the classroom can be helpful. Hearing aids can be used, when clinically necessary.
- **Lonafarnib (Zokinvy).** This oral medicine helps prevent the buildup of faulty progerin and progerin-like proteins in cells. Preventing this buildup in cells can slow the

progression of symptoms that occur in progeria, which can help children live longer. The medicine is approved by the U.S. Food and Drug Administration for children 1 year and older.

- **Low-dose aspirin.** A daily dose may help prevent heart attacks and strokes.
- **Other medicines.** Depending on your child's condition, the health care provider may prescribe other medicines to treat complications. These may include dietary therapy, possibly with statins to help blood vessels and heart function. Also, blood thinners to help prevent blood clots. Medicines to treat headaches and other symptoms may be needed.
- **Physical and occupational therapy.** Physical therapy can help with joint stiffness and hip problems to help your child remain active. Occupational therapy can help your child learn ways to manage daily activities, such as dressing, brushing teeth and eating.
- **Nutrition.** A balanced diet that includes healthy, high-calorie foods can help maintain adequate nutrition. Sometimes nutrition supplements are needed to provide extra calories.
- **Hearing aids.** Although low-frequency hearing loss does not usually affect daily activities, sometimes listening devices or hearing aids are needed.
- **Eye and vision care.** Not being able to close eyelids completely can cause dry eyes and damage to the surface of the eye. Moisturizing eye products and regular vision care can help.
- **Dental care.** Dental problems are common in progeria. Regular visits with a pediatric dentist experienced with progeria can treat problems early.
- dentist experienced with progeria can treat problems early.

CONCLUSION

HGPS is a segmental "premature aging" condition in which children show phenotypes that may reveal information about the aging process at both the cellular and organismal levels. substantial progress has been made in understanding the disease. As the study progresses, HGPS continues to uncover previously unknown aspects of aging. HGPS provides a unique model for clarifying new Lamin A/C and protein roles in the cell. Progeria research has resulted in an increasing number of intriguing treatment possibilities. It is worth noting that in HGPS preclinical investigations, a drug's potential to selectively choose the cardiovascular system should be assessed, as it's the disorder's main function, resulting in premature death. In order to uncover new therapy pathophysiology targets and other outcome metrics, it will be necessary to improve our understanding of disease biology. This will allow us to understand better the damaged pathways that are most relevant to the disease.

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