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HUTCHINSON GILFORD PROGERIA SYNDROME; EPIDEMIOLOGY, CAUSES, CELLULAR MECHANISMS, DIAGNOSIS, COMPLICATIONS AND ADVANCED TREATMENT

L. Amul Thara*[1], K. Rithika[2], M. Ranjith[2], P. Priyadharshini[1], S. Sridhar[1]

[1]Students, SS Institute of Pharmacy, Sankari.

[2]Assistant Professor, SS Institute of Pharmacy, Sankari.

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***Corresponding Author**

L. Amul Thara

Students, SS Institute of Pharmacy, Sankari.

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ABSTRACT

Progeria is a rare genetic disorder that causes premature ageing. It affects the skin, bones, heart, and blood vessels. HGPS usually results from a new point mutation in the LMNA gene, which leads to an alternative splicing defect and produces the mutant protein, progerin. Progerin acts in a dominant-negative way, resulting in various changes at the cellular and molecular levels. These changes include nuclear abnormalities, problems with the DNA damage response, issues with DNA repair, and faster telomere shortening. Interestingly, many signs of HGPS cells resemble those of normal ageing cells. The LMNA mutation leads to the buildup of LMNA which triggers arteriosclerosis, osteoporosis, and cardiovascular problems like heart attacks and strokes. Children with HGPS seem normal at birth but show growth failure by 6-24 months. They experience dwarfism, hair loss, an aged facial appearance (small face, large eyes, beaked nose), prominent scalp veins, skin tightening, joint stiffness, dental crowding, and hearing loss, all while their cognitive development remains normal. This article discussed the current understanding of the molecular pathways that contribute to the pathophysiology of HGPS. It also covers the techniques being tested both in lab settings and in live models to reduce progerin toxicity. Moreover, HGPS cells and preclinical animal models have provided new insights into the disease's molecular and cellular pathways, as well as potential mechanisms related to normal aging. This article explores how progerin expression leads to

HGPS and how the cellular mechanisms and new treatment options for HGPS patients can improve our understanding and management of this condition.

KEYWORDS: Hutchinson-Gilford progeria syndrome, premature aging, progerin, LMNA mutation, progerin toxicity, cellular pathways.

INTRODUCTION

First described by Jonathan Hutchinson in 1886 and Hastings Gilford in 1897, the term "Progeria" means premature aging.[1] It affects about 1 in 4 to 8 million newborns globally, with only around 140 children living with it worldwide.[2] The author describes a child who looked like an old person. His limbs, including fingers and nails, were thin, fragile, and curved backward. Despite being in puberty, he was the same height as a six-year-old. His scalp was very thin and hairless.

Progeria is a laminopathy caused by a mutation in lamin A, which is encoded by the LMNA gene. Lamin a supports the protein complexes that stabilize the cell nucleus and keep the genomes intact. However, when lamin A mutates, it destabilizes the nucleus and damages DNA, causing aging effects. Humans have four major Lamin proteins: Lamin B1, Lamin B2, and Lamins A and C, which are produced by the LMNAB2 and LMNA genes, respectively. These Lamins are intermediate nuclear filaments. Besides providing structure, they paly roles in nuclear functions like chromatin organization, DNA replication, transcription, and cell cycle progression.[3]

Hutchinson-Gilford syndrome has been recognized as a clinical condition for over 100 years. It is classified within a group of progerias caused by mutations in the LMNA gene. This type is distinguished mainly by the age at which the first signs and symptoms appear. Mutations in this gene create a mutant Lamin A protein that deletes 50 amino acids, altering the last cleavage step of pre-Lamin A. The truncates Lamin A, known as progerin, is permanently farnesylated and toxic to cells, resulting in structural and biochemical changes.

Children with progeria have a disproportionately small face compared to their heads, abnormally prominent eyes, a narrow nasal bridge and tip, a small jaw, and crowding or malformation of teeth. Common symptoms also include micrognathia, loss of subcutaneous fat, delayed eruption and loss of primary teeth, irregular skin with small outpouchings over the abdomen and upper thighs, alopecia, nail dystrophy, coxa valga, and progressive joint

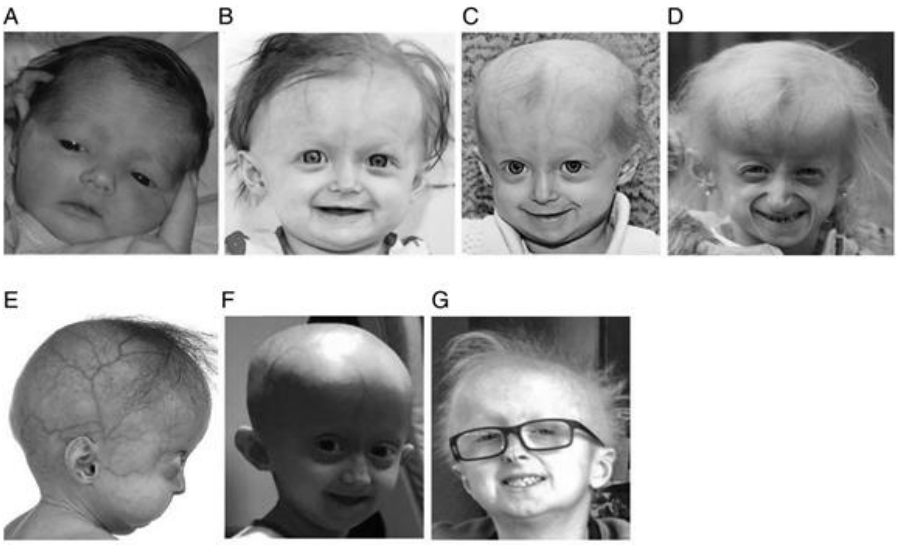
contractures.

Lare, low-frequency conductive hearing loss, dental crowding, and partial absence of secondary tooth eruption were noted. Motor and mental development typically remains normal. Death occurs between the ages of six and 20 due to complications from serious atherosclerosis, either cardiac disease (myocardial infarction or heart failure) or cerebrovascular disease (stroke).

Typical findings include generalized osteopenia, bone resorption around the phalanges and distal clavicle, fish -mouth vertebral bodies, and wide metaphysis with narrowed diaphysis, including coxa valga hip dysplasia. Various craniofacial structures show abnormalities, such as irregular mandibular condyles, hypoplastic articular eminences, optic nerve kinking, and soft tissue changes noted in CT and MRI scans.

Histological findings show that the skin from sclerotic and firms areas resembles early-stage scleroderma with epidermal acanthosis. Thickened collagen bundles appear in the dermis, extending to the subcutaneous tissue. There may be mild perivascular infiltrate, and mucopolysaccharide levels increase. As the disease progresses, subcutaneous fat significantly decreases, and blood vessels become thickened, leading to narrowed vascular lumens.

Lonafarnib is a farnesyltranferase inhibitor that prevents the buildup of defective progerin or progerin-like protein in the body. It received approval in the United States in November 2020 to reduce mortality risk in Hutchinson-Gilford Progeria syndrome (HGPS) and to treat processing- deficient progeroid laminopathies.



OTHERS NAMES FOR THIS CONDITION

- HGPS
- HUTCHINSON-PROGERIA SYNDROME
- PROGERIA
- PROGERIA AND CHILDHOOD

EPIDEMIOLOGY

The reported incidence rate is about 1 in every 4 to 8 million people (3-4).[4] In 2017, the progeria research foundation found 144 cases across 45 countries.[5] Of these, 112 children have classic Hutchinson-Gilford progeria, while 32 have some type of progeroid laminopathy.

Laminopathy

Laminopathies show a wide range old presentations due to genetic differences, due to genetic differences, variable expression, and both complete and incomplete penetrance. One mutation in the LMNA gene that causes HGPS results from a new substitution in exon 11 of LMNA.[6] This mutation activates a hidden splice site and alters the reading frame, leading to the deletion of 50 amino acids at the extreme C-terminal of prelamin A.[7] The abnormal protein produced, called progerin, retains the CAAX motif, becoming farnesylation permanent. This mutant form of Lamin A mainly causes a wide range of abnormalities in nuclear processes.[8] Although c.1824>T is the most frequently reported mutation for the LMNA gene, it has resulted in increased use of this hidden splicing site.

Some of these mutations lead to a more severe phenotype than classic HGPS. Progerin builds up in the nuclear membrane, and these alterations in lamina dynamics change mechanical properties and signaling, affecting signaling, affecting signaling pathways and gene expression. In this way, progericontributes to defects in differentiation and self-renewal in adult stem cells. This results in a faulty extracellular matrix and causes cellular aging. Changes in the internal nuclear membrane leads to immobilization of Lamin A, thickening, and variations in Lamin stiffness, creating lobules or folds in the nuclear envelope.

These damages result in a vulnerable nucleus that is susceptible to physical stress. Type A Lamin A. It also plays a role in organizing higher-order chromatin, forming heterochromatin, and regulating gene expression. Type A Lamin helps bind regions of heterochromatin, known as lamina-associated domains (LADs), to the nuclear lamina. It also interacts with promotor

regions, thereby modulating gene expression during cellular differentiation.

As a result, HGPS nuclei experience a loss of peripheral heterochromatin, a decrease in repressor histone marks H3K9me3, H3K27me3. Changes in histone modification, DNA methylation, chromatin structure, and gene expression related to progerin have all been observed. In HGPS, there is a loss of peripheral heterochromatin and reduced levels of repressor histone modifications (H3K9me3, H3K27me3). Additionally, there is an increase in the transcription of sequences containing pericentromeric repeats. All these changes are noted in older individuals, which is why progerin has been linked to premature aging.[9]

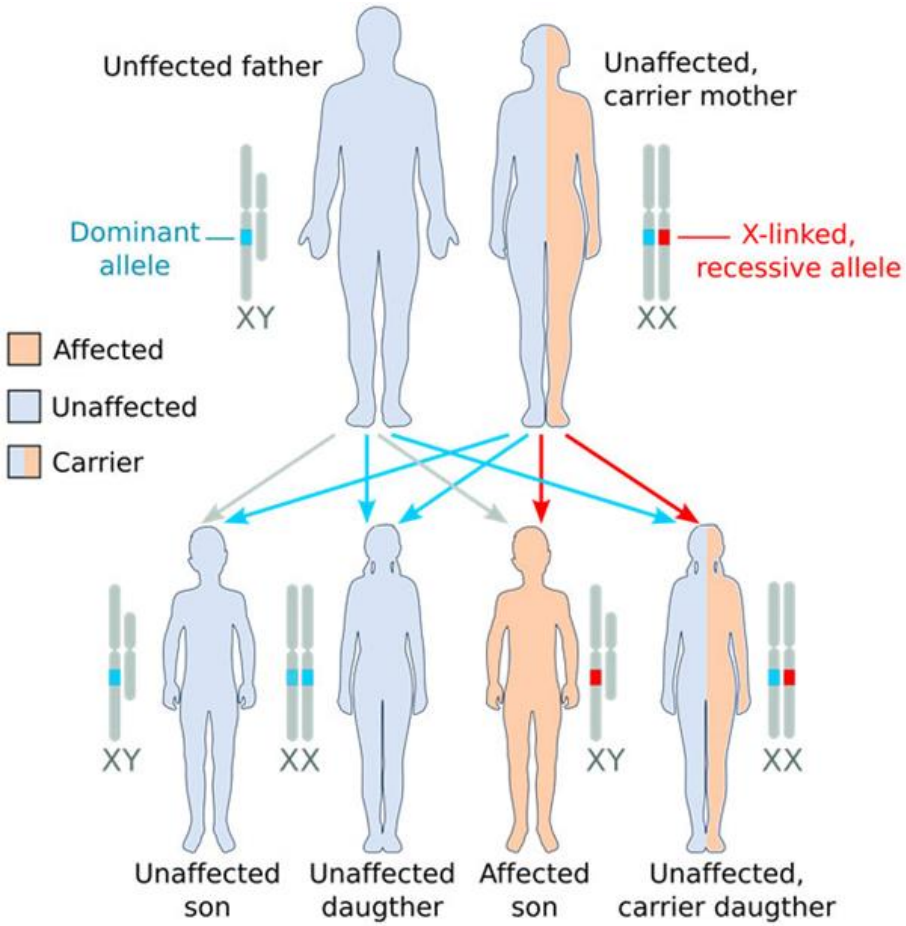
CAUSES

A mutation in the LMNA gene causes Hutchinson Gilford Progeria syndrome. The LMNA gene provides instructions for making a protein is important for determining the shape of the nucleus within cells. It is a key component of the nuclear envelope, the membrane that surrounds the nucleus. Mutations that cause Hutchinson Gilford Progeria syndrome lead to the production of an abnormal version of the Lamin A protein. The altered protein makes the nuclear envelope unstable and progressively damages the nucleus, increasing the chances of premature cell death. Researchers are working to determine how these changes lead to the defining features of Hutchinson Gilford Progeria syndrome.

GENETIC CAUSE

Mutation of LMNE gene

The primary cause is a mutation in the LMNA gene, which codes for Lamin A, a protein essential for the structure of the nuclear envelope, the membrane surrounding the cell's nucleus.



Progerin production

This specific mutation produces a faulty Lamin A protein called progerin. It cannot be formed correctly, leading to its accumulation and damage to the nuclear membrane.

CELLULAR IMPACT

Nuclear Instability

The buildup of progerin makes the nuclear envelope unstable. This causes changes in the nuclear shape and progressive damage.

Accelerated Aging

This cellular damage mimics accelerated aging. It affects tissues under mechanical stress, such as skin, heart, and blood vessels.

INHERITANCE PATTERN

Mostly De Novo

In about 98% of causes, the mutation occurs spontaneously (de novo) in the affected child. It

is not inherited from parents, making HGPS usually sporadic.

Rare Inheritence

In rare cases, it can be passed down from an unaffected parent who carries the mutation in some of their reproductive cells (gonadal mosaicism).

DIAGNOSIS

The diagnosis criteria for HGPS are the recognition of the phenotype combined with a progerin-producing mutation in the LMNA gene. This can occur either at the exon 11 intronic border (a typical form) or within exon 11 (classic form).[12] [HGPS is a fully penetrant autosomal dominant condition, identified by only one mutant LMNA gene it typically arises from a de novo mutation, although one report has documented somatic and gonadal mosaicism.

Sequencing the full coding area and the associated splice junctions can identify both the common mutations in traditional HGPS and the mutations that define a typical HGPS.[13]

Previous case reports revealed synonymous heterozygous variation in the LMNA gene through whole-exome sequencing (WES). Among these variations was a spontaneous and synonymous mutation, C.18224 C> (P.G608G), which could alter the gene's function.

A genetic test for HGPS can reassure parents of affected children that a rare child's condition. Therefore, it is unlikely that any future children will have the same condition.

CELLULAR MECHANISM

Hutchinson-Gilford Progeria syndrome arises from the production of progerin. This truncated Lamin A protein results from a mutation in the LMNA gene. This mutation disrupts the nuclear envelope, causing nuclear blebbing, genomic instability, defects in DNA repair, accelerated telomere shortening, and weakened cell function, including issues with replication and transcription. The buildup of progerin leads to several problems, such as oxidative stress, mitochondrial dysfunction, impaired mechanotransduction, chronic inflammation, and activation of interferon-like responses.[14] These issues ultimately cause premature aging and tissue failure, resembling accelerated normal aging.

Progerin Production And Nuclear Disruption

A specific LMNA mutation leads to alternative splicing, which produces progerin that lacks a

cleavage site. This farnesylated, truncated protein becomes stuck at the inner nuclear membrane. It deforms the nucleus, causing blebs and lobulations, and disrupts the structure of the nuclear Lamina.

Genomic Instability and DNA Damage

Progerin disrupts DNA repair, creates chromosomal abnormalities, and causes replication stress, such as fork stalling. This activated DNA damage signaling pathways like ATM/ATR and increases indicators of DNA damage, such as phosphorylated H2AX.[15]

Epigenetic And Transcriptional Dysregulation

The altered nuclear structure impacts chromatin organization, leading to loss of heterochromatin and changes in gene positioning. This results in mis-regulated gene expression and affects essential processes like transcription and cell division.

Telomer Dysfunction

Progerin speeds up telomere attrition, which is a hallmark of aging. This contributes significantly to premature cellular senescence.[16]

Cellular Stress Ans Signaling

There is an increase in reactive oxygen species (ROS) and oxidative stress. The immune responses are activated, such as the CGAS/STING pathway, leading to chronic inflammation and interferon-like responses. Cellular responses to mechanical stress, particularly in vascular cells are impaired.

Metabolic and Mitochondrial Issues

There is a disruption in glucose and lipid metabolism along with compromised mitochondrial function. These combined defects lead to premature cell aging (senescence), stem cell exhaustion, and severe vascular and connective tissue problems observed in HGPS.[17]

HGPS AND ITS COMPLICATIONS

HGPS complications can be life-threatening and have a high mortality rate. They range from severe cardiovascular issues to neurological problems and skeletal abnormalities. Stunted growth is common, while mental retardation is rare.

Cardiovascular Complication

HGPS is marked by rapid aging and a swift progression into heart disease. Fibrosis and

increased progerin production in coronary arteries make the condition worse. The most common echocardiographic changes are extensive atherosclerosis and electrophysiological shifts.[18]

About 90% of deaths in HGPS results from heart attacks. Heart failure arises from ongoing low-grade inflammation and high oxidative stress.[18] Key processes tied to cardiovascular aging include changes in chromatin, problems with the endothelium, mitochondrial oxidative stress, and genomic instability.

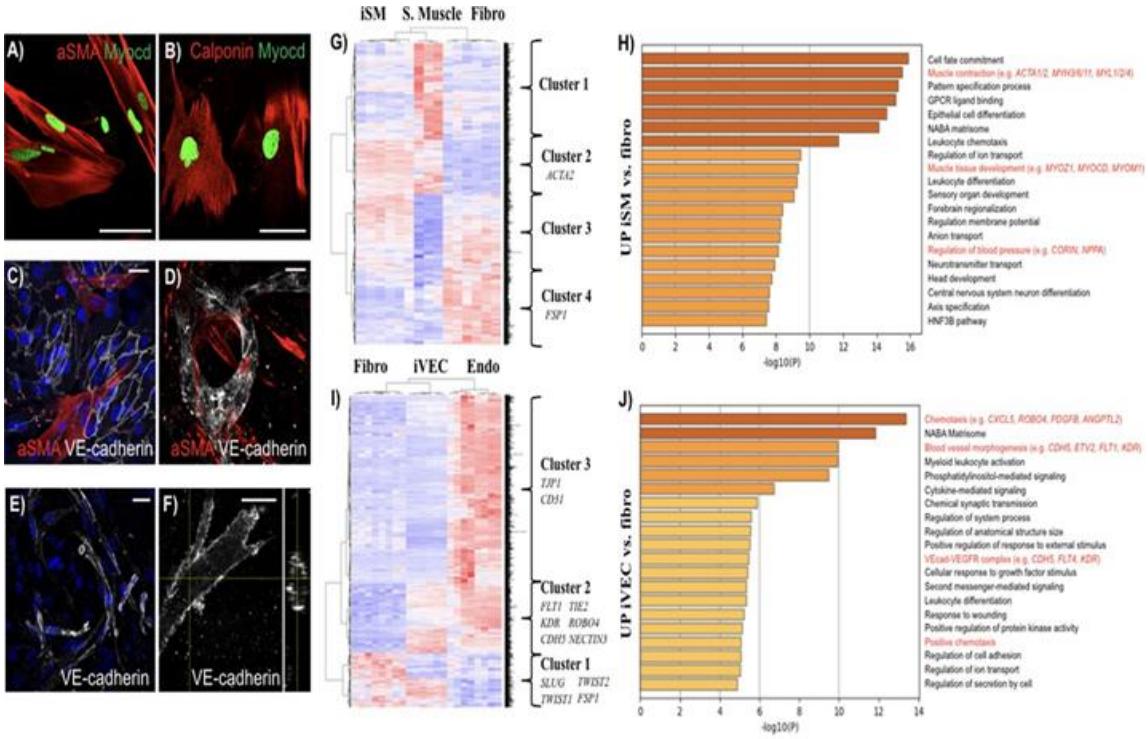
HGPS causes serious cardiovascular issues mainly due to progerin buildup, which affects both heart electrical signals and blood vessel structure. Common cardiac electrical issues include bradycardias, heart block, and ventricular irregularities. These issues often stem from myocardial fibrosis, which disrupts normal electrical flow.

Autonomic dysfunction worsens these changes, resulting in linger QT intervals and a higher risk of sudden cardiac death. Chronic low-doses paclitaxel has shown promise in partially reversing some of these heart problems, offering potential treatments for the electrical issues related to HGPS.

Vascular calcifications are another key feature of extracellular pyrophosphate, a strong inhibitor of calcification. These calcifications often appear in major arteries and worsen as the vessel walls stiffen.[19] Treatment approaches that focus on pyrophosphate metabolism, such as adenosine triphosphate (ATP)- based therapies paired with agents like levamisole and ARTL67156, have shown positive results in preventing vascular calcifications and extending lifespan in mouse models of HGPS. Furthermore, progerin buildup leads to significant loss of vascular smooth muscle cells, adding to vessel stiffening and further heart issues. Antisense oligonucleotide therapies, like PPMO SRP-2991, have proven effective in lowering progerin levels, restoring VSMC numbers, and enhancing heart health in animal studies.

Besides these specific treatments, various therapeutic approaches are being explored to tackle the cardiovascular aspects of HGPS. These include gene editing methods aimed at fixing the genetic mutation that causes progerin production, along with small molecules and medications designed to lessen the effects of progerin buildup.

These new therapies offer hope for better heart health and survival chances for HGPS patients, who face a high risk of early death from cardiovascular problems.



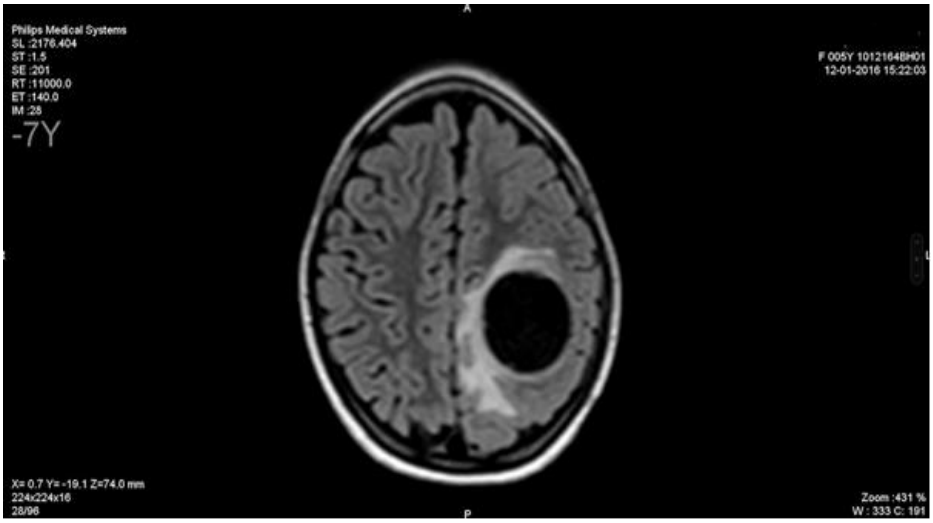
Neurological Complication

Blood flow and vascular issues may cause damage to the nervous system. However, most progeria patients do not experience neurological problems. The absence of vascular disease may be due to the miR-9 gene, which limits the activity of Lamin-A and progerin. Although HGPS is linked to quicker aging, typical aging symptoms, such as dementia and cognitive decline, rarely appear.[20]

Many patients experience severe headaches, muscle pains, or seizures duo to reduced blood flow and vascular problems. Most headaches resemble migraines.

Neurodegenerative disorders show a reduction in autophagic activity. Recent findings suggest that the cellular and molecular processes involved in Parkinson's disease overlap with those in HGPS. Therefore, individuals with HGPS may have an increased risk of developing Parkinson's disease.

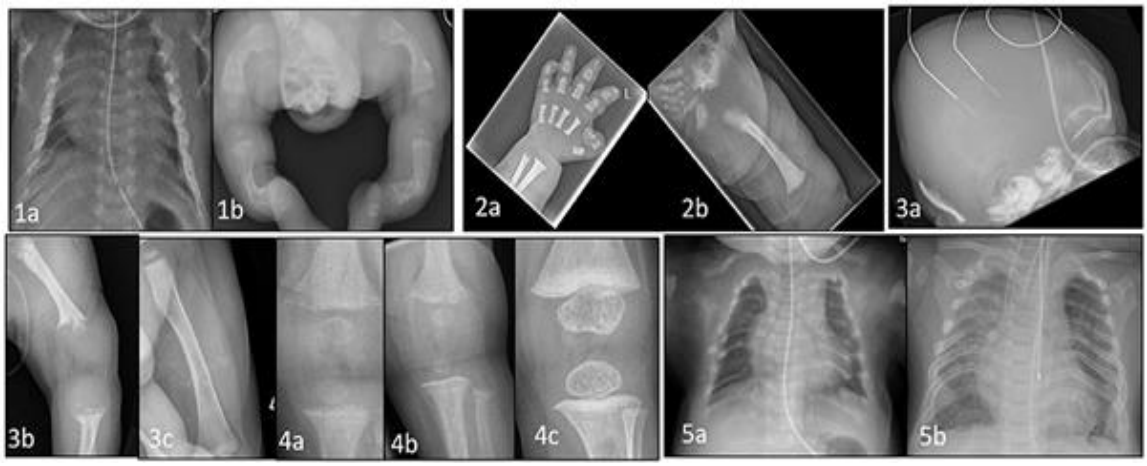
Other commonly reported neurological issues include partial seizures, paralysis, hemiplegia, and speech difficulties. Most patients do not have long-lasting symptoms; however, some may experience dizziness and weakness in their limbs.



Skeletal Abnormalities

Hutchinson-Gilford Skeletal Dysplasia is characterized by typical bone and joint issues in progeria patients. Some abnormalities include narrow ribs, small collarbones, and acro-osteolysis. Bone density decreases, and there is greater demineralization at the ends of long bones in HGPS. A vascular necrosis arises from blood flow issues, particularly in the femoral head. Skeletal problems in HGPS may involve changes in the jaw and skull, suggesting possible defects in bone growth, especially in limbs.

Patients with HGPS face major orthopedic issues like osteolysis, osteoporosis, skeletal dysplasia, and delayed healing after fractures and surgeries. Other symptoms include hip dislocation and changes in the femoral head. In classic HGPS, osteolysis can affect the mandible, skull, collarbones, and fingers. In non-classical HGPS, osteolysis is more severe. Osteolysis occurs via changes in bone development, affecting bones in the arms and proximal sections of fingers. Fractures often occur in the skull, ribs, and arms in non-classical progeria. Aging associated with HGPS leads to deterioration of facial bones due to reduced sizes of the jaw, causing overcrowded teeth. The frontal, parietal, and sphenoid regions of the skull often sow changes. A decrease in chin size by age two, narrowing shoulders, and gradual shrinkage of the upper body are common physical features.[21] Joint mobility declines, particularly in wrists, shoulders, hips, and ankles, causing a shuffling walk later in life. X-ray findings In HGPS include various bone abnormalities, open sutures thin or missing collarbones, and changes in long bones, likely due to underlying issues with collagen or an unknown active resorption process.



ADVANCED TREATMENT

Research on advanced treatment for HGPS now involves trying to correct the defective progerin protein, and the first FDA- approved drug, Lonafarnib (Zokinvy), targets the farnesyltransferase enzyme and has been shown to reduce progression and improve survival.

1. FARNESYLTRANSFERASE INHIBITORS
2. LONAFARNIB
3. TRIPLE THERAPY
4. DRUGS ACTIVATING AUTOPHAGY
5. GENETIC THERAPY
6. SUPPLEMENTATION THERAPY

Farnesyltransferase Inhibitors

Many strategies are being explored for treating HGPS. Anticancer compounds known as farnesyltransferase inhibitors (FTIs) have been found to reduce markers in progeria fibroblast cultures and symptoms in progeroid mice. FTI are small molecules that attach reversibly to the CAAX binding part of farnesyltransferase, preventing progerin from farnesylating and integrating into the nuclear membrane.

Lonafarnib

Lonafarnib (zokinvytm) is an oral FTI introduced by Eiger Bio-Pharmaceuticals. The FDA approved it in 2020 to treat progeria, progeroid laminopathies, and hepatitis D infections. The FDA approved lonafarnib for treating processing- deficient progeroid laminopathies and for reducing mortality from HGPS.[22] Lonafarnib can cause gastrointestinal tract (GIT) issues, but these may be reduced with a dose of 115 mg/m2 twice daily taken with breakfast and dinner. After four months, the dose can be increased to 150 mg/m2 twice daily. There are no

available dosage forms of lonafarnib for patients with a body surface area less than 0.39 m2. Lonafarnib also improved weight-bearing capacity, bone fracture resistance, hearing conditions, and cardiovascular stiffness; however, some individuals experienced significant weight gain.

Lonafarnib also enhanced cardiac health in children with HGPS, which is crucial since cardiac damage leads to high mortality rates. After treatment, peripheral arterial stiffness improved, evident from echo dense common carotid arteries and increased pulse wave velocity before treatment. Low-level sensorineural hearing also showed improvement. Many clinical trials have shown that FTIs can lead to an increase in prelamin A levels and are usually well-tolerated, with side effects mainly related to the gastrointestinal tract.

Triple Therapy

A large clinical trial with 45 patients with HGPS tested a combination of lonafarnib, pravastatin, and zoledronate therapy. This study found that blocking progerin and the geranylgeranylation and farnesylation of prelamin A can prevent HGPS symptoms. Additionally, zoledronate helps prevent osteoporosis while pravastatin slows down atherosclerosis progression. About 71.0% of participants met the outcome criteria, showing improvements in carotid artery echodensity and or weight gain. Lonafarnib alone and in combination with other therapies in HGPS resulted in an average survival increase of 1.6 years.[23]

DRUG ACTIVATING AUTOPHAGY

Rapamycin (Sirolimus)

Rapamycin, a blocker of the mammalian target of rapamycin, was one of the first treatment strategies to focus on progerin turnover. Rapamycin improves the unusual shape, helps clear progerin through autophagy, delays cellular aging, and maintains chromatin structure in HGPS fibroblasts in culture. Like in HGPS, rapamycin shows potential in several models of neurodegenerative disease.[24]

Everolimus

Everolimus, a rapamycin analog, increases autophagy to help break down harmful, insoluble aggregates like progerin. It also improves the growth of cell lines and delays cellular aging, even when the usual HGPS mutation is absent. Although using lonafarnib alone for these specific donor traits was limited, combining lonafarnib with Everolimus had a positive effect

on SMC proteins and Vaso activity. Overall, the results suggest that treatment with these two drugs offers more benefits than using either one alone. However, finding the right dosage is essential for effective treatment.

Sulforaphane

This antioxidant, found in many cruciferous vegetables, boosts progerin release through autophagy and reverses cellular features of HGPS in the lab. The combination of sulforaphane and lonafarnib showed a gradual and synergistic effect on activating autophagy in HGPS fibroblast cultures, even at harmful levels.

MG132

MG132 is a proteasome inhibitor that can promote progerin clearance in HGPS patients. Proteasome inhibitors have improved progerin clearance through macro-autophagy in HGPS patient fibroblasts, IPSC-derived mesenchymal stem cells, and vascular smooth muscle cells. Researchers also found that this compound can indirectly reduce the increase of prelamin A is HGPS cell types.

GENETIC THERAPY

CRISPR Therapy

Genetic methods like CRISPR therapy offer new ways to reduce progerin production. HGPS is a great candidate for genetic therapy because fixing a single-point mutation can greatly improve symptoms. Antisense morpholino-based therapy uses oligomers that attach to specific nucleotide sequences to stop the translation of mRNA. This approach, which blocks harmful LMNA G609G progeric mice.[25] Another study found that antisense oligonucleotide (ASO) treatment increased Lamin C production while lowering progerin levels. ASO treatment in mice also decreased progerin expression in tissues, suggesting a potential therapeutic use for ASOs in HGPS. Two recent papers have shown the benefits of CRISPR therapy in living organisms for the first time. As this technology improves, theses therapies are likely to become even more effective.

Adenine Base Editing

Adenine base editors (ABEs) change A-T base pairs to G-C without breaking DNA strands. This methos allows for accurate correction of mutations. In progeria, the dominant- negative mutation in the LMNA gene (c.1824C>T) causes the production of progerin, a harmful protein. ABE treatment can fix this mutation, allowing normal RNA splicing and lowering

progerin levels. In mouse models, ABE treatment greatly improved vascular health and increased lifespan from 215 to 510 days, showing its potential as a treatment for HGPS.

Remodelin

Remodelin, an N-acetyltransferase-10 (NAT10) inhibitor effective in progeria models, leads to chromatin compaction while fixing nuclear abnormalities, growth issues, and DNA damage typical in progerin-expressing cells. Several studies are currently tracking the effects of remodelin on gene expression and exploring its potential as a treatment.

Gut Fecal Microbiota

Fecal microbiota transplantation is one of the most interesting and recent developments in treating progeria. Barcena et al. discovered intestinal dysbiosis in two progeria mouse models and in HGPS, characterized by lower levels of Verrucomicrobia and higher levels of proteobacteria and Cyanobacteria. Adding fecal microbiota from wild-tpe mice to progeria mice improved both lifespan and overall health, providing support for microbiome-based therapy for HGPS.

SUPPLEMENTATION THERAPY

Vitamin D

Changes in vitamin D and vitamin D receptor (VDR) status significantly affect cells and organisms and are associated with various disorders. It shows aging traits in VDR knockout mice similar to those seen in patients with Hutchinson-Gilford Progeria syndrome (HGPS), such as early hair loss, growth delays, muscle wasting, ear disease, and shorter lifespans. According to Kreienkamp et al., the buildup of progerin is connected to lower levels of VDR and DNA repair factors like BRCS1 and 53BP1. Reinstating VDR signaling through 1, 25-dihydroxy vitamin D3(1,25D) in HGPS fibroblasts may help reduce issues like nuclear abnormalities, double-strand break repair defects, and early aging. Therefore, vitamin D may help repair DNA damage and relieve stress in rapidly dividing progeric cells.

Growth Hormone Treatment

The HGPS mouse model (Zmpste24-/-mice) shows a significant drop in plasma insulin-like growth factor1(IGF-1). Bringing IGF-1 levels back to normal with recombinant human IGF-1 and growth hormone (GH) increased lifespan. Additionally, there was a noticeable improvement in several HGPS traits, such as hair loss, increased subcutaneous fat, less kyphosis, and better body weight.

Retinoids

Retinoids are currently awaiting in vivo testing. Retinoids acid-responsive elements (L-RARE) in the LMNA gene promotor lower the gene's expression in response to all-trans retinoic acid (ATRA) treatments. The combination of ATRA and rapamycin showed a synergistic effect on progerin breakdown in HGPS fibroblast cells.

Limitations

HGPS is rare genetic disorder caused by mutations in the LMNA gene, leading to progerin production that speeds up aging. Symptoms include growth delays, and early signs of aging. Treatments like FTI (e. g, Lonafarnib) help improve heart health and bone strength, while gene therapies such as CRISPR aim to fix the genetic flaw. Other therapies, including activating autophagy and GH supplementation, also show promise. Despite encouraging results, these treatments are still experimental and need more clinical validation to confirm their effectiveness.

CONCLUSION

HGPS causes rapid aging in children due to mutations in the LMNA gene. This leads to symptoms such as hair loss, wrinkled skin, and heart problems by school age. The condition affects 1 in 4 to 8 million births, and the average lifespan is about 14.5 years. There is no cure, although symptoms can be managed.

Ongoing trials are testing farnesyltransferase inhibitors like lonafarnib, which can modestly extend life, as well as gene therapies that focus on reducing progerin buildup. It is important to provide multidisciplinary care to improve the quality of life for those affected.

Future research has the potential to bring breakthroughs in anti-aging for everyone. We should push for more funding and awareness to help families impacted by this condition around the world.

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