A REVIEW ON PROGERIA AND AGING

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Abstract:

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare genetic disorder caused by mutations in the LMNA gene, leading to the abnormal protein progerin, which accelerates aging. First described in 1886, HGPS presents symptoms like growth retardation, hair loss, and severe atherosclerosis, typically resulting in early death. Progerin disrupts nuclear integrity, causing morphological changes, genomic instability, and cellular decline, paralleling processes seen in natural aging. Studies have shown progerin's presence in both HGPS patients and aging individuals, suggesting overlapping mechanisms. Recent bioinformatics and RNA-Seq analyses have highlighted differentially expressed genes linked to both progeria and natural aging, such as KRT8, KRT18, and IGFBP2, which may contribute to aging and disease. Additionally, epigenetic changes common to both forms of aging have been identified, underscoring their role in the aging process. Therapeutic strategies, including vitamin D3 supplementation, have shown potential in reducing progeria levels and alleviating HGPS symptoms, while possibly also slowing aging in non-HGPS individuals.

HGPS and Werner Syndrome (WS) are two disorders resembling accelerated aging, with HGPS linked to LMNA mutations affecting lamin processing and DNA damage, particularly at telomeres, and WS associated with mutations in the WRN helicase gene. Both conditions share features of natural aging, such as increased DNA damage and vascular issues. While DNA damage, especially at telomeres, is crucial in these syndromes, not all LMNA mutations lead to instability. Research indicates that human aging involves two primary mechanisms: telomere shortening, leading to cellular senescence, and DNA damage, contributing to genomic instability. These mechanisms, influenced by p53 status, interact to enhance genomic instability and promote aging characteristics.

Key Words:*1.Human aging 2. Werner syndrome 3. Hutchinson progeria syndrome 4. Aging 5. Lamin.*

Introduction:

Aging and death are inevitable in an organism's life cycle, prompting significant research into the biological processes behind aging, particularly focusing on nuclear metabolic defects that lead to mutations and DNA damage. A notable condition linked to aging is progeroid syndrome, characterized by premature aging features. The first documented case of progeria appeared in 1886, described by Hutchinson, who initially categorized it as a form of ectodermal dysplasia. In 1895, Hastings Gilford provided a detailed account of the condition, coining the term "progeria," meaning "before old age" in Greek. Progeria is a rare, lethal genetic disorder with an incidence of approximately one in four million live births,

with around 100 cases recorded. Affected individuals typically live to about thirteen years, although some reach their late teens or early twenties, with very few living into their forties. The condition is primarily caused by a point mutation and is generally not inherited, though there are exceptions.

Progeroid syndromes, such as Hutchinson-Gilford progeria syndrome (HGPS), are genetic disorders that mimic aspects of aging and are primarily caused by mutations in DNA repair or nuclear lamina genes. HGPS is linked to mutations in the LMNA gene, leading to the production of progerin, a truncated form of lamin A. This syndrome results in premature aging-like pathologies, particularly affecting mesenchymal tissues like the skeleton, muscles, and cardiovascular system, with affected individuals typically dying in their early teens from complications such as stroke or heart disease. The nuclear lamina, composed mainly of lamin A, plays a crucial role in maintaining nuclear structure and regulating genetic processes. In HGPS fibroblasts, nuclear morphology deteriorates with cell passages, showing increasing anomalies such as lobulations and thickened lamina, while control cells exhibit far fewer abnormalities. Notably, late-passage HGPS cells lose heterochromatin and show abnormal clustering of nuclear pore complexes. Injecting progerin into normal cells quickly induces HGPS-like nuclear changes, but normal lamin A does not reverse these effects, indicating progerin's dominant negative impact on nuclear architecture.

Aging is a time-dependent decline in physiological functions, contributing to major health issues like cardiovascular diseases, diabetes, neurodegenerative disorders, and cancer. López-Otín et al. (2013) proposed the hallmarks of aging to enhance understanding in biogerontology, but Gems and de Magalhães (2021) noted that these hallmarks do not fully encompass aging's complexity. Interconnected aging processes necessitate further research, including meta-analyses and omics studies to reveal age-related pathways. "Omics" disciplines, starting with genomics, provide comprehensive assessments of biological molecules. For example, transcriptomics analyzes RNA levels, facilitating insights into aging-related diseases. A notable case is Hutchinson-Gilford progeria syndrome (HGPS), linked to a mutation in the LMNA gene, which results in the production of the truncated protein progerin. Research and clinical trials led by the Progeria Research Foundation have progressed treatments for HGPS. Fleischer et al. (2018) used fibroblast RNA sequencing data from progeria patients and healthy individuals to create a computational method for predicting biological age. Their dataset, available publicly, has been widely cited and utilized in various studies on aging. This study contributes a comparative analysis of aging in nonagenarians and progeria patients against healthy children, highlighting its significance in ongoing research in both aging and bioinformatics.

Epidemiology:

Hutchinson-Gilford Progeria Syndrome (HGPS) has a prevalence of 1 in 4-8 million births and is generally considered

sporadic, with around 114 diagnosed cases globally. The average lifespan is about 13.5 years, with death often resulting from cardiovascular issues. Key symptoms include growth retardation, alopecia, skin atrophy, and notable cognitive abilities that remain intact.

HGPS is primarily caused by a de novo autosomal dominant mutation, while atypical forms may follow an autosomal recessive inheritance pattern. Affected children appear normal at birth but show significant growth failure within the first year, leading to characteristic physical features and health issues like joint stiffness and high blood pressure. Biochemically, they exhibit elevated low-density lipoproteins and increased urinary hyaluronic acid levels.

Children with HGPS biologically age approximately ten years for each calendar year, developing heart disease at a rate comparable to a typical 60-year-old by age 13. Despite their severe symptoms, their intelligence remains unaffected, and further research is needed to understand brain signaling pathways in these patients. Only one individual has been reported to survive to 45 years of age.

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare genetic disorder occurring in approximately one in four million births, with 148 known patients affected with progeria living around the world as of March 2017. In the U.S., its incidence is one in eight million. The disease predominantly affects white individuals (97%), while black Americans represent only 3%. The male-to-female ratio of patients is 1:1.5. Progeria is typically not heritable, as affected individuals usually die before reaching reproductive age. Genetic studies suggest it results from a sporadic autosomal dominant mutation in the LMNA gene. There have been rare instances of healthy parents being carriers of this mutation, and only a few families with multiple affected members have been documented, often associated with older paternal age.

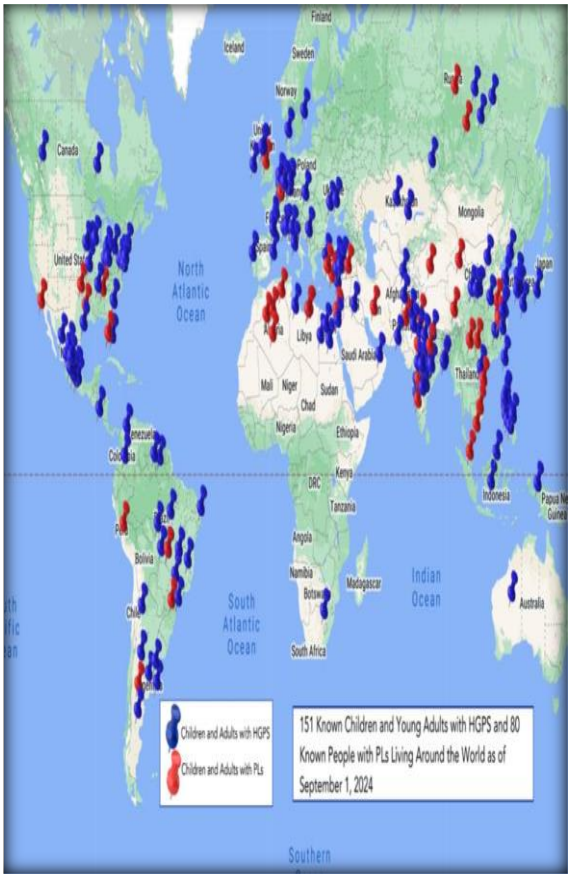

Fig no. 1. This figure shows the 151 known children having progeria around the world, and all of them have a progerin producing mutation in the LMNA gene, and 80 among them are in the progeroid laminopathy category but do not produce progerin.

Pathophysiology of Aging:

Aging is a complex developmental process that begins at conception and progresses until death, influenced by both genetic and environmental factors. Unlike disease, which tends to increase in prevalence with age, aging itself is not classified as a disease. The aging process is characterized by a decline in cell proliferation, where normal cells eventually cease to divide and die, contrasting with cancer cells that continue to proliferate unchecked. Accumulated DNA damage is a significant contributor to aging and age-related diseases. Research suggests that chronic energy restriction may extend lifespan across various species, although the mechanisms behind this are still not fully understood.

Various theories attempt to explain aging, including the idea that random mutations in somatic cell DNA accumulate over time, increased cross-linking of proteins like collagen due to glucose interactions, and oxidative damage from free radicals, with longer-lived species often having more protective enzymes against such damage. Additionally, there may be a biological clock regulating aging processes in mammals, potentially located in the hypothalamus, which operates through hormonal pathways.

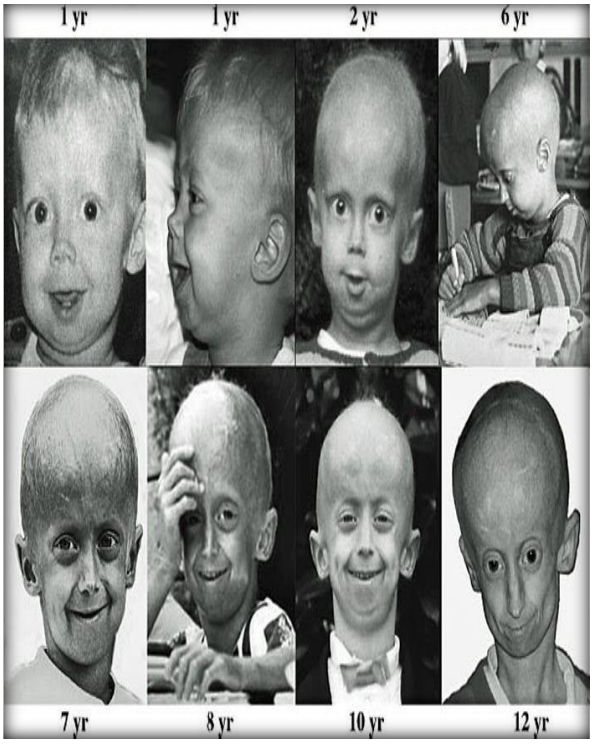

Fig no. 2. progeria patient at the age of 1 year, 1 year, 2 year, 6 year, 7 year, 8 year, 10 year, 12 year.

Hutchinson-Gilford progeria syndrome (HGPS) serves as a poignant example of accelerated aging, with patients displaying clinical features such as rapid atherosclerosis in both cerebral and coronary arteries. Notably, HGPS is characterized by a unique lipid profile, with the only significant abnormality being decreased levels of high-density lipoprotein cholesterol, distinguishing it from typical age-related arteriosclerosis. Patients with HGPS experience a range of symptoms, including loss of subcutaneous fat and muscle, skin atrophy, osteoporosis, arthritis, poor growth, and alopecia. Skeletal dysplasia is also common, manifesting as structural abnormalities in bone strength and geometry. Extensive lipofuscin deposition, a marker of

aging, is evident in multiple organs, including the kidneys, brain, liver, and heart.

The underlying pathology of HGPS stems from defects in lamin A, an essential protein of the nuclear membrane involved in maintaining nuclear integrity, DNA repair, gene expression regulation, and telomere stability. These defects result in genomic instability, decreased cell proliferation, and premature cell senescence and death. The abnormal protein, progerin, is a truncated version of prelamin A, caused by mutations in the LMNA gene. Notably, mutations in LMNA are associated with not only HGPS but also other premature aging syndromes and muscular dystrophies. A consistent pathological finding in HGPS is the marked loss of vascular smooth muscle cells in major blood vessels, leading to sclerosis and fibrosis. Patients often develop features akin to normal aging, such as cardiovascular disease characterized by accelerated vascular stiffening and peripheral vascular occlusive disease. Interestingly, progerin has been observed to accumulate in cultured fibroblasts from normally aged individuals, reinforcing the idea that aging may involve similar processes of cellular damage and dysfunction. Ultimately, the pathophysiology of HGPS is driven by the presence of progerin and its detrimental effects on lamin A function, rather than merely the absence of normal lamin A, highlighting the intricate relationship between genetic factors and the aging process.

Molecular Aspects:

Progeria is a rare genetic disorder characterized by accelerated aging, particularly exemplified by Hutchinson-Gilford progeria syndrome (HGPS). This condition results from mutations in the LMNA gene, leading to the production of an abnormal protein called progerin, which disrupts normal cellular function and nuclear stability. Research in the last two decades has advanced our understanding of progeria and its implications for the broader study of aging.

HGPS affects approximately 1 in 4 to 8 million births globally, with a life expectancy of about 13.5 years. Patients typically exhibit growth failure, alopecia, and skin changes, while maintaining normal cognitive abilities. The disorder is primarily caused by de novo mutations, and affected children generally appear healthy at birth before showing symptoms within their first year.

Other progeroid syndromes, such as Werner syndrome and Cockayne syndrome, share similar features but differ in genetic causes and inheritance patterns. For instance, Werner syndrome is caused by mutations in the WRN gene and manifests in early teenage years, while Cockayne syndrome involves mutations in DNA repair genes.

The LMNA gene mutations in HGPS lead to significant nuclear shape abnormalities, which are linked to various diseases known as laminopathies. Progerin's effects extend beyond structural changes, impacting cellular stability and DNA repair mechanisms. Recent therapeutic approaches, such as the farnesyltransferase inhibitor Lonafarnib, have shown promise in alleviating some symptoms of HGPS.

Overall, progeria and its related syndromes provide insights into the aging process, highlighting the roles of genetic mutations, cellular dynamics, and potential therapeutic avenues. Continued research is crucial for unraveling the complex mechanisms underlying these disorders and improving patient outcomes.

Diagnosis:

How is progeria diagnosed?

Your child's healthcare provider may be able to diagnose your child's condition based on their physical appearance. They'll perform a physical exam and ask about your child's symptoms. If they suspect progeria, they can use genetic testing to confirm the diagnosis. The test requires taking a blood sample from your child.

Diagnosis may be established by the following:

- Characteristic clinical features.
- Classical geriatric disorder of the young.
- Thin, high-pitched voice.
- Typical gait and coxa valga.
- Radiography of the skull: craniofacial disproportion, delayed and abnormal dentation
- Radiography of the hands: radiolucent terminal phalanges.
- Urine test: excessive excretion of the Glycosaminoglycan, hyaluronic acid.
- Culture of skin fibroblast exhibited 76.1% DNA repair capacity compared with normal.
- Genetic: sporadic dominant mutation.
- Arterial biopsy: premature atherosclerosis And subintimal fibrosis.

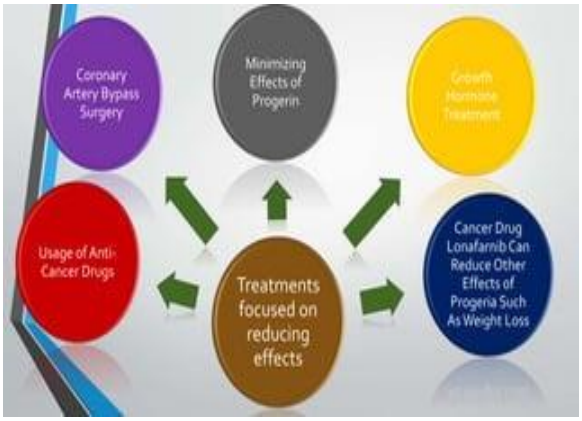

Fig no. 3. Treatment focused on reducing effects

What are the symptoms of progeria?

Progeria symptoms look like the signs of normal aging in human beings, but they occur at a much younger age. Starting within the first two years of life, children with progeria begin to show signs and symptoms of rapid aging that include:

- Growth failure/short stature.
- Wrinkled skin.
- Balding.
- Stiff joints with decreased range of motion.
- Tough skin that resembles scleroderma.
- Loss of body fat.

Craniofacial abnormalities may include:

- A large open soft spot on the head (fontanelle).
- Narrow face for the size of their head (macrocephaly).

- Beaked nose.
- Teeth that come in late (delayed eruption).
- Small (underdeveloped) jaw (micrognathia).

As the condition advances, less obvious symptoms may begin to develop. These include:

- Hip dislocation.
- Cataracts.
- Arthritis.
- Plaque buildup in the arteries.

Hutchinson-Gilford Progeria Syndrome (HGPS) is linked to several health issues, including gait abnormalities and osteoporosis, which can lead to repeated fractures from minor injuries. Additional symptoms may include a distinctive high-pitched voice, absence of breast or nipple development, lack of sexual maturation, hearing loss, and various other abnormalities.

Children as young as five may experience significant thickening and reduced elasticity of arterial walls, particularly affecting major blood vessels like the coronary arteries and the aorta. This can result in cardiomegaly (enlarged heart) and abnormal heart sounds (murmurs) due to disrupted blood flow. Throughout childhood and adolescence, progressive arteriosclerosis can cause chest pain from insufficient oxygen to the heart (angina), blocked blood flow to the brain (cerebrovascular occlusion), heart failure due to the heart's inability to pump effectively, and localized heart muscle damage (myocardial infarction). These cardiovascular issues can lead to serious, life-threatening complications in early life.

Standard Therapies for Hutchinson-Gilford Progeria Syndrome (HGPS)

In November 2020, the FDA approved Zokinvy (lonafarnib), a farnesyltransferase inhibitor initially developed for cancer, as the first treatment for HGPS. It is now available by prescription in the U.S. and through Eiger Biopharmaceutical's Managed Access Program in several other countries.

Prior to this approval, treatment with Zokinvy was limited to children enrolled in clinical trials through the Progeria Research Foundation at Boston Children's Hospital. Over 90 progeria patients have been treated with Zokinvy in four clinical trials since 2000.

In April 2018, findings from an observational cohort study supported by the Progeria Research Foundation showed a reduced mortality rate in patients treated with Zokinvy compared to untreated individuals. Earlier, in September 2012, the first clinical trial demonstrated that Zokinvy was effective, with every child exhibiting improvements in areas such as weight gain, hearing, bone structure, or notably, increased blood vessel flexibility.

Beyond Zokinvy, managing HGPS involves addressing individual symptoms through a collaborative approach. A multidisciplinary team may include pediatricians, orthopedists, cardiologists, physical therapists, and other healthcare professionals to create a tailored treatment plan.

Symptomatic and supportive therapies are crucial for individuals with HGPS. For instance, those experiencing chest pain from inadequate oxygen supply to the heart (anginal attacks) may receive specific medications to alleviate these symptoms.

What causes progeria?

Hutchinson-Gilford progeria syndrome (HGPS) results from a single nucleotide mutation in the gene on chromosome 1 that produces lamin A, leading to the production of the abnormal protein progerin. HGPS typically arises sporadically and is not inherited; it occurs due to a new autosomal dominant mutation. The likelihood of having a child with progeria is about 1 in 4 to 8 million for parents without a history of the condition, while the risk increases to 2-3% for those who have already had an affected child, due to mosaicism in one parent.

The precise mechanisms behind the accelerated aging in HGPS remain unclear. Researchers propose that ongoing cellular damage, exacerbated by free radicals generated during metabolic processes, contributes to this accelerated aging. Antioxidant enzymes, which normally help mitigate such damage, may be less active in individuals with HGPS. Studies have shown that fibroblasts from HGPS patients exhibit significantly reduced levels of key antioxidant enzymes, such as glutathione peroxidase and catalase, compared to healthy individuals, indicating a need for further investigation.

Moreover, progerin is produced in small amounts by healthy individuals but accumulates in coronary arteries with age, suggesting its potential role in atherosclerosis and heart disease. This connection between normal aging, cardiovascular issues, and progeria highlights the importance of researching progerin, as understanding and treating progeria may also benefit those affected by age-related diseases like heart attacks and strokes.A genetic mutation in the LMNA gene causes progeria. The LMNA gene is responsible for making a protein called lamin A.

Lamin A is an important part of the structural scaffolding that holds the nucleus of each cell in your body together. A tiny mutation in the LMNA gene causes it to create an irregular form of the lamin A protein called progerin. Progerin takes the place of the lamin A and makes the nuclei of your cells unstable, slowly damaging them.

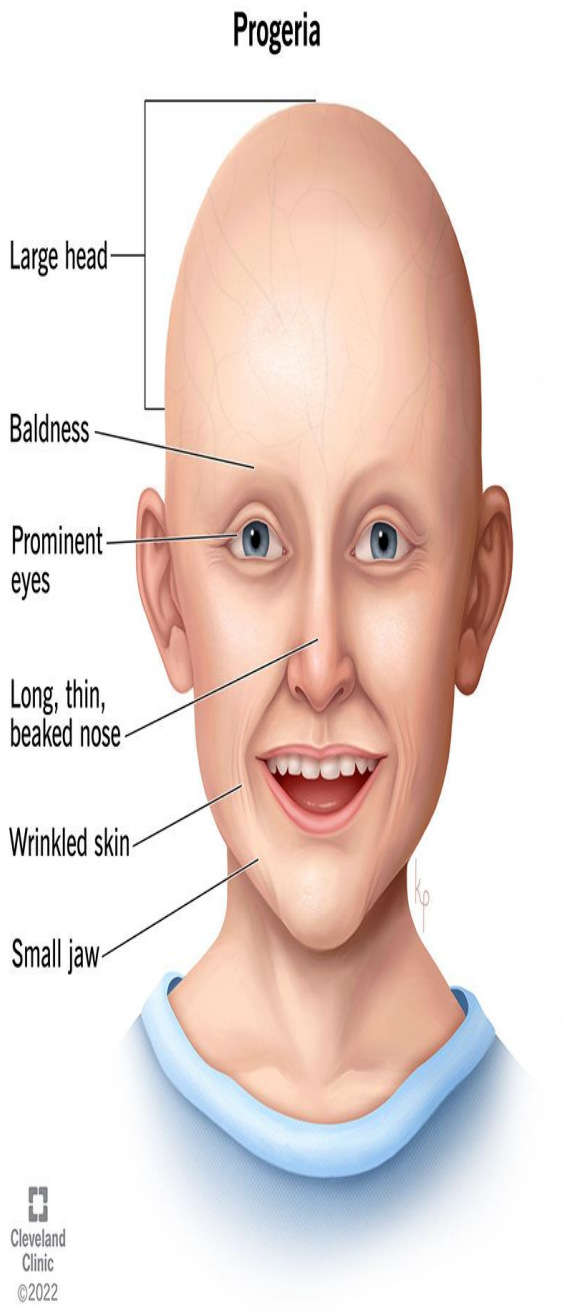

Fig no.4. Signs of progeria look like normal aging but at a much younger age.

Treatment:

1. There's no cure for progeria, but researchers are working on finding one. One clinical trial is looking at a kind of cancer drug, FTIs (farnesyltransferase inhibitors), to see if it can help slow the disease.

2. Treatments can help ease or delay some of the disease's symptoms.

3. Medication and diet changes. Your child's doctor may suggest drugs and changes to your child's diet to lower cholesterol or prevent blood clots. A low dose of aspirin every day can help prevent heart attacks and stroke. Growth hormone can help build height and weight. The FDA has approved lonafarnib to prevent the buildup of defective progerin, which can affect the heart.

4. Physical and occupational therapy can help your child keep moving if they have stiff joints or hip problems.

5. Surgery. Some children may have coronary bypass surgery or angioplasty to slow the progression of heart disease.

6. At home. Kids with progeria are more likely to get dehydrated, so they need to drink plenty of water, especially when they're sick or it's hot. Small meals more often can help them eat enough, too. Cushioned shoes or inserts can ease discomfort and encourage your child to play and stay active.

7. Sunscreen. Use a broad-spectrum sunscreen with an SPF of at least 15. Reapply it every 2 hours, or more if your child is sweating or swimming.

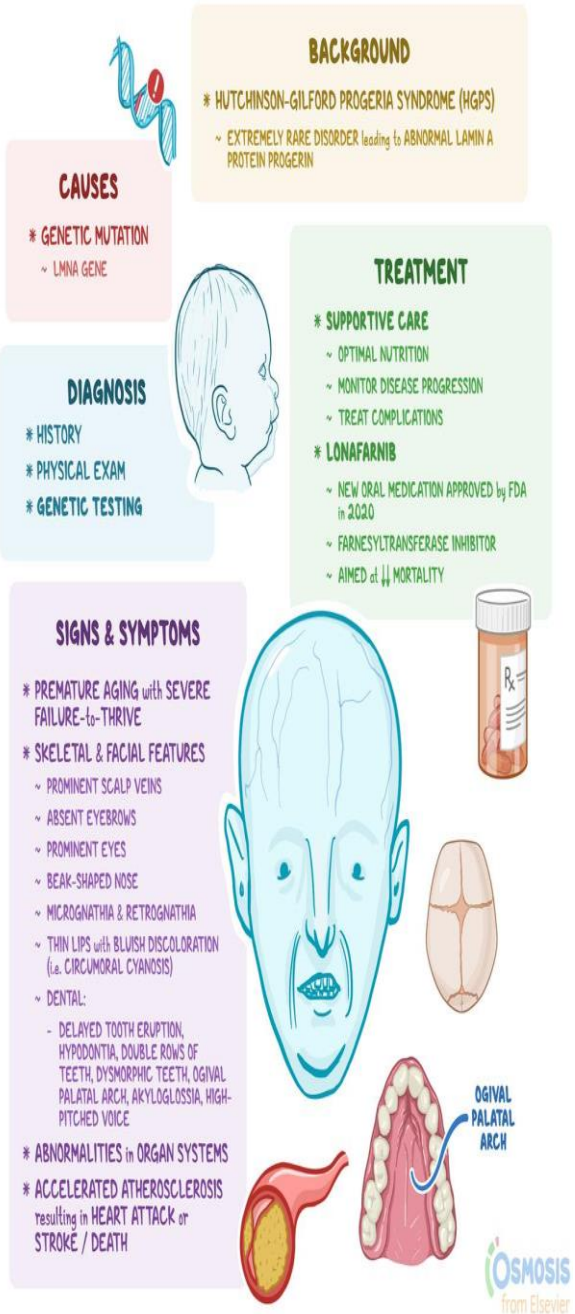

Fig no. 5. Sign, symptoms, treatment, background and treatment of Progeria.

Progeria and Aging:

Aging and progeria are interconnected, with evidence linking the speed of aging to telomere length. Telomeres, which are repetitive sequences (TTAGGG) at the ends of chromosomes, shorten with each cell division. Once they reach a critical length, cells enter senescence and stop dividing. Individuals with progeria have notably short telomeres and typically experience aging-related changes in skin, muscle, and cardiovascular and nervous system cells, leading to a mean lifespan of about 13 years due to heart-related complications. Although their physical appearance resembles that of the elderly, progeria patients maintain cognitive abilities typical for their chronological age.

Syndrome	Mutation in gene	Clinical symptoms
Hutchinson-Gilford progeria syndrome	*LMNA*[4,5]	Growth retardation mostly evident within a year of birth, skin atrophy, alopecia, osteolysis, cardiovascular complications, *etc.*
Werner's syndrome	*WRN*[17]	Symptoms appear mostly during early teenage years; development of cataract, atherosclerosis, skin atrophy, osteoporosis, *etc.*
Trichothiodystrophy or Tay's syndrome	*ERCC2*, *ERCC3* or *GTF2H5*[18]	Growth and mental retardation, congenital ichthyosiform erythroderma, brittle hair.
Cockayne's syndrome	*ERCC6*; *ERCC8*[19]	Growth failure, atypical photosensitivity, impaired development of the nervous system, poor cognitive skills, loss of hearing and visual abilities, *etc.*
Dyskeratosis congenita	*DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *TIN2* or *TCAB1*[16]	Nail dystrophy, abnormal skin pigmentation, mucosal leukoplakia and pulmonary complications.

Source: Refs 3-5,12,16,18,19

Fig no. 6. Summary of gene mutations leading to various progeroid syndromes with their clinical symptoms.

Progeria is linked to impaired DNA repair mechanisms and is classified as an autosomal

recessive disorder. The exact cause of aging-related peripheral neuropathy remains unclear. Some inherited defects in genome maintenance processes lead to accelerated aging in specific tissues, including neurodegeneration. Research suggests that the murine model of XFE progeroid syndrome arises from reduced levels of the ERCC1-XPF DNA repair endonuclease, which contributes to peripheral neuropathy. This indicates that DNA damage may act as a stochastic factor driving age-related degenerative changes

Scope of future research:

The awareness of Hutchinson-Gilford Progeria Syndrome (HGPS) has increased due to efforts by various research groups and the Progeria Research Foundation (PRF). While elevated levels of hyaluronan (HA) were initially suggested as a specific marker for HGPS, some studies have contradicted this, showing that HA levels in HGPS patients are similar to those in controls. Research by Gordon et al. utilized both quantitative and qualitative methods to analyze serum and urinary hyaluronidases, questioning the reliability of HA as a diagnostic marker. Consequently, the quest for a definitive diagnostic marker continues.

The GH/IGF-1 axis has long been associated with longevity. Research indicates that DNA damage can suppress this axis, contributing to progeroid symptoms. Further exploration of DNA damage mechanisms in HGPS and aging may illuminate connections between the two. Studying the interactions of the LMNA gene with other aging-related genes in animal models could enhance our understanding of HGPS pathogenesis. The PRF maintains a Cell and Tissue Bank with 121 cell lines available for research, which could aid in unraveling the mechanisms behind HGPS and other progeroid syndromes. This understanding could extend to various fields, including molecular biology, cellular senescence, mitochondrial physiology, oncology, and dermatology, benefiting not only those affected by progeroid syndromes but also patients with cardiovascular diseases, cancer, and other degenerative disorders.

Proteins associated with HGPS may significantly influence the aging process, potentially increasing the risk of early heart disease in affected children. When examining the effects of IGF-1 signaling and other hormonal pathways in existing aging models, notable deviations from normal parameters have been observed. These deviations may arise from dysfunctions in the pituitary or other organs, micronutrient metabolism issues, abnormal protein glycation, or other physiological processes. For instance, WNIN/Ob obese rats demonstrate premature aging, tumor development, and immune response deficiencies. Analyzing these animal models for genomic, proteomic, and biochemical abnormalities may reveal shared pathways that contribute to these conditions.

Conclusion:

The field of gerontology has gained prominence in recent years as researchers focus on delaying the aging process and its associated physical, psychological, and social challenges. Hutchinson-Gilford Progeria Syndrome (HGPS) has a known

inheritance pattern but often presents sporadically, making it important to explore the cellular and molecular mechanisms that accelerate aging and exacerbate the disease.

For centuries, humans have sought ways to slow aging, but its complexity poses challenges for intervention. With age-related diseases now leading causes of mortality in developed nations, there is a clear imperative to target aging itself to mitigate these conditions. Research indicates that genes involved in key biological pathways can influence the aging rate in model organisms, supporting the notion of multiple aging causes. Investigations into the biology of aging often focus on extending an organism's maximum lifespan, as this implies a connection to the aging process. Additionally, studying progerias like HGPS offers unique insights into normal aging mechanisms that may not be evident through invertebrate models.

The discovery that the mTOR inhibitor rapamycin can extend mouse lifespan, even when administered late in life, exemplifies targeting aging to address age-related diseases. This prompts the question of whether such a drug could benefit progeroid mice. If HGPS's molecular pathology mimics an accelerated aging process, then therapies aimed at slowing normal aging might also be effective for these conditions. Although rapamycin's role in anti-aging remains uncertain, it represents one of the first potential candidates, paving the way for future treatments as research progresses.

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