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Review

Hutchinson–Gilford progeria syndrome: unraveling the genetic basis, symptoms, and advancements in therapeutic approaches

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***Abstract*:** Hutchinson–Gilford Progeria syndrome (HGPS) serves as a prominent model for Progeroid syndromes, a group of rare genetic disorders characterized by accelerated aging. This review explores the genetic basis, clinical presentation, and complications of HGPS. HGPS is caused by mutations in the LMNA gene, resulting in the production of a defective structural protein, prelamin A. This protein contains a "CAAX" motif, where C represents cysteine, and its abnormal processing is central to the disease's pathology. HGPS leads to multiple organ systems being affected, including cardiovascular, skeletal, neurological, and dermatological systems, causing severe disability and increased mortality. Cardiovascular issues are particularly significant in HGPS and are crucial for developing therapeutic strategies. Recent advances in treatment modalities offer promise for managing HGPS. Farnesyltransferase inhibitors and genetic interventions, such as CRISPR-Cas9, have shown potential in mitigating progerin-associated symptoms, with encouraging results observed in preclinical and clinical studies. Additionally, emerging therapies such as rapamycin, sulforaphane, and MG132 hold promise in targeting underlying disease mechanisms. Comprehensive management approaches, including growth hormone therapy, retinoids, and dental care, are emphasized to enhance overall patient well-being. Despite progress, further research is essential to unravel the complex pathophysiology of Progeroid syndromes and develop effective treatments. Continued focus on therapies that address progerin accumulation and its downstream effects is vital for improving patient care and outcomes for individuals affected by HGPS and related disorders. This review highlights ongoing efforts to understand and combat Progeroid syndromes, aiming to alleviate the burdens imposed by these debilitating conditions.

Plain language summary

Progeroid syndromes: unraveling the genetic basis, multifaceted symptoms, and advancements in therapeutic approaches

This comprehensive review delves into the intricate landscape of Progeroid Syndromes, focusing on the Hutchinson-Gilford Progeria Syndrome (HGPS) and its atypical forms. From the genetic underpinnings involving the LMNA gene to the myriad of symptoms affecting various organ systems, the article illuminates the pathophysiology and disease progression of HGPS. It outlines the spectrum of complications spanning cardiovascular, skeletal, neurological, skin, oral health, and growth abnormalities seen in patients. Furthermore, it highlights the emerging therapeutic approaches, from farnesyltransferase inhibitors to genetic therapies like CRISPR, providing hope for managing this rare and challenging condition.

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Introduction

Progeroid syndrome, abbreviated as PS, is a group of rare and life-threatening autosomally dominant hereditary conditions characterized by early aging. Genotypically, Hutchinson–Gilford Progeria syndrome (HGPS) is divided into two types: the classic HGPS and the atypical HGPS.[1]

The disease is named after two researchers, Hasting Gilford and Jonathan Hutchinson; however, the disease and its progression remain poorly understood.[2] Approximately 300–400 children are diagnosed with progeria with a global prevalence of one in 4 million live births worldwide.[3,4]

HGPS presents with a wide range of symptoms, and the hallmark of the disease is very early aging[5] with an expected average life span of about 15 years. HGPS is progressive, and death from vascular events may occur before 10 years.[6,7] The exact pathophysiology of HGPS is poorly understood. Pathogenic variants in the LMNA gene can lead to multiple problems such as accelerated telomere shortening, disruption of gene expression, chromatin structure changes, mitochondrial dysfunction, abnormalities in nuclear membrane morphology, and defective alternative splicing and DNA repair.[8] HGPS victims encounter shortened Lamin A precursor build up in the nucleus leading to nuclear disruption.[9] Vascular alterations and early atherosclerosis are associated with progeria's musculoskeletal symptoms.[10]

Mutations in the LMNA gene, results in the synthesis of faulty lamin A and C,[11,12] leading to the synthesis of a hazardous protein termed progerin, which induces telomere shortening, genomic instability, aberrant nuclear morphology, and dysregulated gene expression in in vitro animal models.[11] Replication stress further exacerbates this genomic instability, triggering innate immune responses and hastening aging.[13,14]

Furthermore, a systemic component linked to progeria's advancement is the somatotropic axis's dysregulation.[12]

Symptoms include a distinctive face, prominent eyes, leg and scalp veins, a senile appearance, loss of eyebrows, eyelashes, and scalp hair, stunted growth, and sclerodermatous changes (Figure 1).[5] It is brought on by a mutation in the LMNA gene, which results in the build-up of progerin, an abnormal version of the nuclear membrane protein Lamin A. Children die primarily from premature atherosclerotic cardiovascular disease as a result of this accumulation, which leads to a wide range of disease phenotypes. With an emphasis on creating therapies and a cure for this illness, the Progeria Research Foundation has been at the forefront of research and clinical trials.[15]

Diagnosis

Phenotype recognition combined with a progerin-producing mutation in the LMNA gene, either at the exon 11 intronic border (atypical form) or within exon 11 (classic form), is the diagnostic criteria for HGPS. HGPS is a fully penetrant autosomal dominant condition for which only one LMNA gene is identified. HGPS is usually generated by a de novo mutation, although one case of somatic and gonadal mosaicism has been reported.[16] Both the common mutation of traditional HGPS and the mutations defining atypical HGPS can be found by sequencing the full coding area and the splice junctions that are connected with it.[17] The LMNA gene displayed synonymous heterozygous variation in previously studied case reports, as revealed by whole-exome sequencing (WES). Among these variations was a spontaneous and synonymous mutation C.1824 C>T (P. G608G), which could change the gene's function (Figure 2).[18]

Parents of affected children can be reassured by this genetic test for HGPS that a rare genetic mutation causes their ailment. As a result, it is improbable that any future offspring would have the condition.[19]

HGPS and its complications

HGPS complications can be life-threatening, with a high mortality rate. Complications range

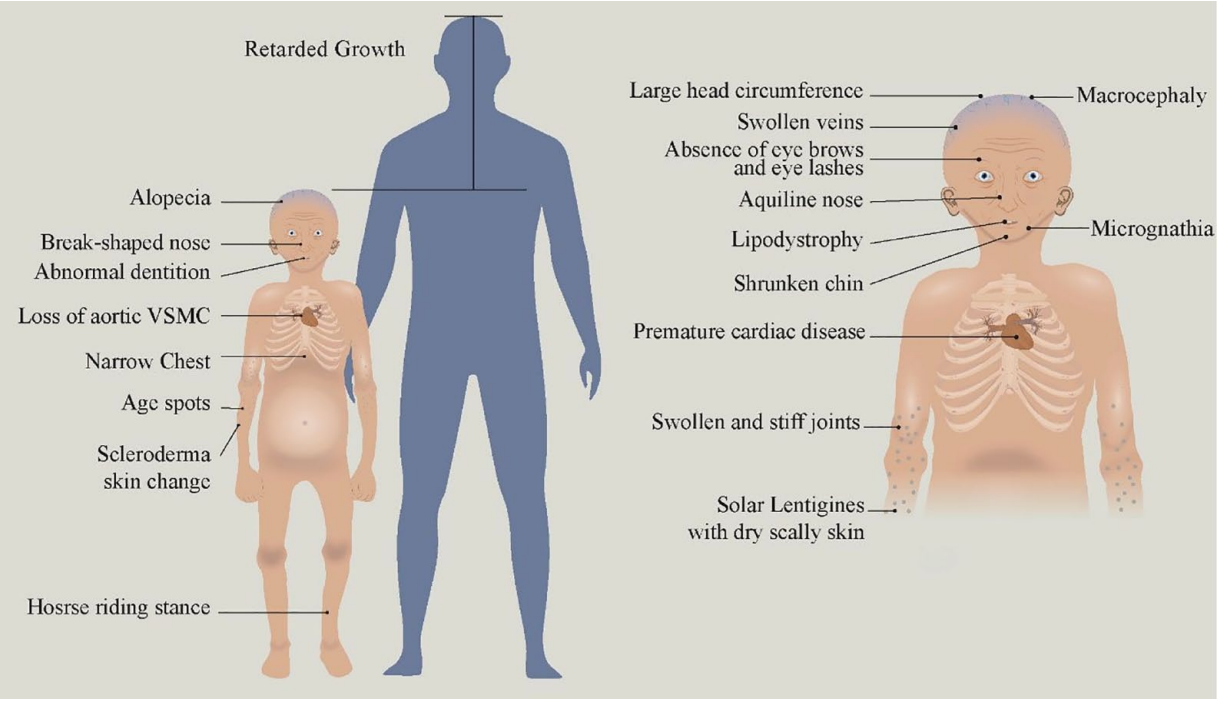

Figure 1. Clinical manifestations of HGPS.
HGPS, Hutchinson–Gilford Progeria syndrome.

from severe cardiovascular abnormalities, neurological manifestations, and changes in oral health and dentition. Stunted growth is common and mental retardation is rare.

Cardiovascular complication

HGPS is characterized by dramatic premature aging and quick and accelerated progression into cardiovascular disease,[20] fibrosis and increased progerin generation in coronary arteries further worsen the disease.[21] Extensive atherosclerosis and electrophysiological changes are the most prevalent ecocardiographic anomalies.[22,23]

A total of 90% of deaths in HGPS occur from cardiac infarctions. Heart failure develops in HGPS as a result of chronic low-grade inflammation and excessive oxidative stress.[24] The processes linked to cardiovascular aging include chromatin remodeling, endothelial dysfunction, mitochondrial oxidative stress, and genomic instability.[25,26]

HGPS leads to severe cardiovascular complications, primarily due to progerin accumulation, which affects both cardiac electrophysiology and vascular integrity. Cardiac electrophysiological disturbances, including bradyarrhythmias, heart block, and ventricular arrhythmias, are common in HGPS, often driven by myocardial fibrosis that disrupts normal electrical conduction. These changes are exacerbated by autonomic dysfunction, leading to prolonged QT intervals and increased susceptibility to sudden cardiac death.[21,27] Chronic low-dose paclitaxel has shown potential in partially reversing these cardiac defects, offering a therapeutic pathway to mitigate some of the electrophysiological issues associated with HGPS.[28]

Vascular calcifications are another hallmark of HGPS, driven by a deficiency in extracellular pyrophosphate, a potent inhibitor of calcification. These calcifications are prevalent in major arteries and are exacerbated by the stiffening of the vessel walls. Treatment strategies targeting pyrophosphate metabolism, such as adenosine triphosphate (ATP)-based therapies combined with inhibitors like levamisole and ARL67156, have shown promising results in preventing vascular calcifications and extending longevity in

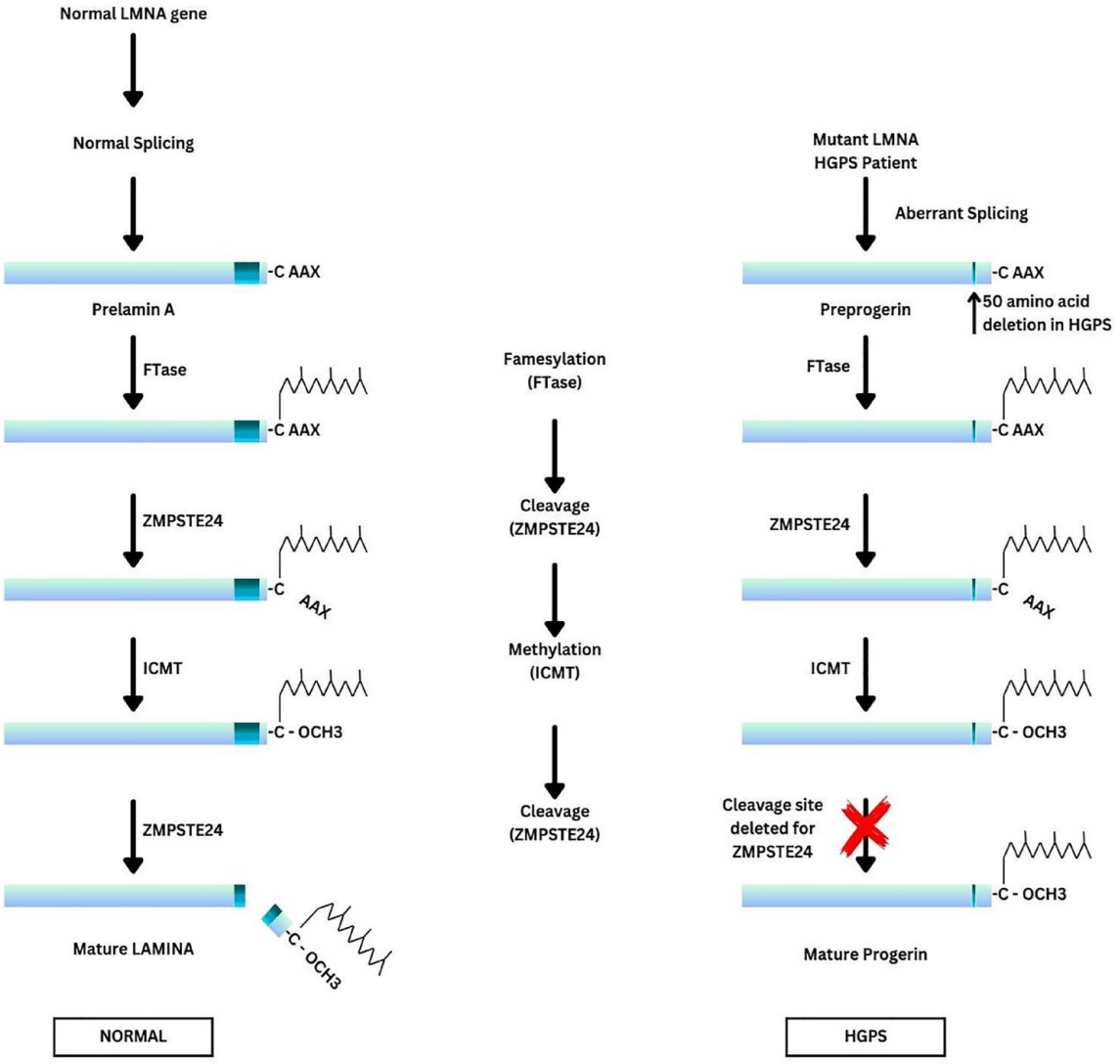

Figure 2. Mutant LMNA-induced diseased progression.

mouse models of HGPS.[29] Moreover, progerin accumulation leads to significant loss of vascular smooth muscle cells (VSMCs), which contributes to vessel stiffening and further cardiovascular complications. Antisense oligonucleotide therapies, such as PPMO SRP-2001, have shown efficacy in reducing progerin levels, rescuing VSMC loss, and improving cardiovascular outcomes in animal models.

In addition to these specific interventions, a variety of therapeutic strategies are under exploration to address the cardiovascular manifestations of HGPS. These include gene editing techniques aimed at correcting the genetic mutation responsible for progerin production, as well as small molecules and pharmacotherapy designed to mitigate the downstream effects of progerin accumulation. These emerging therapies offer hope for improving both cardiovascular health and overall survival in patients with HGPS, who are at high risk for early mortality due to cardiovascular complications.

Skeletal abnormalities

Hutchinson–Gilford Skeletal dysplasia is a syndrome of typical bone and joint abnormalities in progeria patients. Some of the anomalies include narrow ribs, small clavicles, and acro-osteolysis.

Bone density decreases and greater demineralization occurs at the ends of long bones in HGPS. Avascular necrosis is due to vascular impairment, especially in the femoral head.[11] Skeletal abnormalities associated with HGPS can involve mandibular and cranial dysplasia with haphazard growth, possibly implicating osteogenesis defects, particularly in extremities.[30]

Major orthopedic problems faced by HGP patients manifest as osteolysis, osteoporosis, skeletal dysplasia, and delayed bone healing after fractures and osteotomies. Further symptoms include hip dislocation, avascular changes in femoral capital epiphyses, and osteoarthritis.[11,30,31] In classical HGPS, one can observe osteolysis on the mandible, neurocranium, viscerocranium, clavicles, and distal phalanges. On the other hand, osteolysis is more severe in nonclassical progeria. Osteolysis involves bone formation via enchondral bone development, which also apply to long bones of the upper limb and proximal sections of distal phalanges. In nonclassical progeria, fractures often occur not only in the skull but also in the ribs and humerus. The aging process associated with HGPS also causes decay of facial bones due to a reduction in the size of the maxilla and mandible, leading to overcrowded teeth.[32] The frontal, parietal, and sphenoid parts of the skull often show mottling.[33] A decrease in chin size up to 2 years, narrowing shoulders, and gradual narrowing of the upper half body are characteristic physical features. Joint mobility decreases, especially in wrists, shoulders, hips, and ankles, leading to shuffling gait at later stages.[32] Radiographic changes in HGPS include multiple intramural bones, open sutures persistency, partially or totally resorbed clavicles, thin ribbon-like with partial resorption, and probably deficient posterior segments. Sclerotic changes with a decreased corticomedullary ratio and pathological fractures are also documented in long bones, possibly due to underlying abnormalities in collagen structure or an active resorption process of unknown origin.[30]

Neurological complications

Vascular problems and malfunctions may damage the nervous system. However, in most patients with progeria, the nervous system is unaffected. Absence of vascular disease and malfunctions may be due to the miR-9 gene, which limits the activity of lamin-A and progerin. HGPS is associated with quicker aging, but symptoms of progressing age, such as senile dementia and cognitive inability, do not usually occur.[34]

Due to poor flow of blood and damage to vascular physiology, many patients experience severe headaches, myalgia, or seizures. Most of the headaches present with symptoms similar to migraine.[23]

Neurodegenerative disorders seem to exhibit impaired autophagic activity. Recent studies reveal that cellular and molecular mechanisms in Parkinson's disease and neurodegenerative disorders HGPS are similar. Therefore, HGPS increases the risk of developing Parkinson's disease.[35]

Other commonly occurring neurological abnormalities include partial seizures, paralysis, hemiplegia, and dysarthria. Most patients don't experience long-lasting symptoms; however, a few may experience vertigo and limb weakness.[32]

Dermatological abnormalities

Early signs of HGPS involve changes to the skin,[11] such as sclerotic skin (77.8%), which appears 1 month after birth. Common variations include patches of discoloration, stippled pigmentation, and constricted areas that limit movement. Scleroderma alterations over the abdomen and lower extremities give the skin a dimpled look with uneven pigmentation.[11] Normal to atrophic epidermis and a rise in the basal layer of melanin usually occur.

The nails deteriorate, and the skin over the phalanges typically turns red and inflamed. Blood vessels become prominent due to the loss of subcutaneous fat and skin thinning. The thin facial skin can wrinkle significantly.[32] Nocturnal lagophthalmos is caused by tighter skin and less fat around the eyes, which increases the risk of corneal dryness and keratitis-induced opacification of the lens.[36] Sclerodermoid alteration, prominent scalp veins, prominent body veins, circumoral cyanosis, and dyspigmentation are five important categories of skin disorders.

Hair colors in HGPS include blonde, brown, and black or dark. Hair texture varies between normal, coarse, delicate, and thin. A zone of discolored skin can occasionally mark the border

between normal and sclerodermatous skin. The skin becomes atrophic, thin, and dry, with diminished turgor, minor scaling, and occasionally shows hyperkeratosis. Thin scalp skin, clearly visible and frequently enlarged veins, and alopecia are common, except for a few delicate, curling, downy hairs. Hair fall occurs between 6 months and 2 years. most children are bald between the ages of 2 and 3 but rarely, hair fall is insignificant up to 12–15 years. Mostly eyelashes drop off. With very few exceptions, body hair turns lighter in color. (chest, legs, and arms).[32]

Oral health and dentition

Oral anomalies include hypodontia, ankyloglossia, ogival palate, double rows of teeth, and delayed tooth eruption (both primary and permanent teeth), including both upper and lower sets. Circumoral cyanosis also occurs in HGPS.[19,37] Teeth become crowded as the maxilla and mandible grow smaller and are positioned erratically. Tooth eruption is significantly delayed in HGPS with micrognathia.[32,38,39]

Jaws

The mandible has an obtuse mandibular angle and a short ramus. The alveolar process is atrophic, whereas the palatal vaults are high and narrow. Because the maxillary arch is short, there is a general craniofacial imbalance.[40]

Teeth

Primary molars' roots develop improperly and incompletely, whereas the crowns of permanent teeth calcify slowly and unevenly. Lateral incisors are palatally and lingually positioned.[40] Tooth discoloration also occurs.[37,40]

Eye, speech, and hearing

Patients experience keratopathy and hyperopia.[27] The loss of intra-orbital fat makes the eyes appear more prominent. Nystagmoid motions in the eyes are unusual, with corneal clouding and iridocorneal adhesions.[32] Hyperopia and astigmatism occur. Eyes appear large because of the relatively delayed growth of facial bones,[36,37] short eyelids and recurring corneal ulcers.[41]

Reduced lingual power, range of motion, and labial weakness are common.[27] Voice is often high-pitched. Advancing age does not lower the pitch.[37]

Hearing loss is typical in HGPS.[32] High-frequency sensorineural hearing loss, tympanograms.[27] Low-tone conductive auditory loss is common in HGPS and is a sign of stiff tympanic membranes and deficiencies in the middle ear's bone and ligamentous components.[36] Many patients also experience low-frequency hearing loss due to middle ear abnormalities and ear canal aberrations, projecting ears without ear lobe, patients with a shorter ear canal, and patients with stiff auricular cartilage.[11,42,43]

Growth

The distinctive build-up of progerin that is not soluble in the cytoplasm. Weaknesses include reduced growth, a shortened lifespan, nuclear blebbing, and progerin, which builds up as a person ages.[44]

In newborns with HGPS, the mean birth weight is lower. Growth delay begins during pregnancy, and weight gain was more disturbed than height gain. The average person by the age of 10 is 138 cm tall, whereas the patient with HGPS by age of 10 is approximately 100 cm indicating a stunted growth . Prepubertal or pubertal growth spurts don't exist. Development of secondary sexual traits is extremely uncommon; pubic and axillary hair growth, as well as breast development, are practically nonexistent. The penis could be slightly small or have regular male genitalia, entire lack of spermatogenesis. The female genitalia, both external and internal, were reported to be normal, except for an adult's hypoplastic labia—a single giant ovarian cystadenoma and several small to large follicular ovarian cysts. Mensuration is followed by an erratic cycle.[32,45]

No nipples were reported to exist in Hutchinson's, only "scar-like patches."[37] The recognized mean age of menarche in healthy females without HGPS (about 14.5 years of age) is not significantly different from the average menarche age.[46] Menarche was noted despite undetectable leptin levels, consistent with their low body fat percentage.[47]

There have been no reports of aberrant thyroid, parathyroid, pituitary, or adrenal gland function[37] though some individuals progressed to Tanner developmental stage II (the stage of minimal penis and testicular enlargement; moreover, formation of breast buds and pubic hair occurs. Patients typically have an upbeat, nimble demeanor, and normal psychological development.[11]

Treatment

Farnesyltransferase inhibitors

Many strategies are being considered for treating HGPS. Anticancer molecules called farnesyltransferase inhibitors (FTIs) have been found to assuage markers in progeria fibroblast culture, and symptoms in progeroid mice.[8,48,49] FTI restores nuclear morphology in the above HGPS models.[50] FTIs are small molecules that attach reversibly to the CAAX binding segment of farnesyltransferase,[51] preventing progerin from farnesylating and intercalating into the nuclear membrane (Figure 3).[52–55]

Lonafarnib. Lonafarnib (zokinvytm), an orally active FTI, (introduced by Eiger BioPharm aceuticals FDA approval in 2020.) combats progeria, progeroid laminopathies, and infections by hepatitis D virus.[56] US FDA approved lonafarnib for treating processing-deficient progeroid laminopathies and to lower mortality from HGPS.[57] lonafarnib-induced gastrointestinal tract (GIT) problems may be minimized at a dose of 115 mg/m^2 twice daily with breakfast and dinner. After 4 months, the dose may be raised to 150 mg/m^2 twice daily. No dosage forms of lonafarnib are available for patients with a body surface area <0.39 m^2.[56] Lonafarnib also improved weight-bearing capacity and fracture-resistance of bones, audio logical conditions, and cardiovascular stiffness, but significant weight gain occurred in a few.[52,58]

Lonafarnib also provided symptomatic improvement in cardiac status in children with HGPS with significant outcomes because cardiac damage is the main reason for death. Peripheral arterial stiffness improved after treatment, as seen by echo dense common carotid arteries and significantly higher pulse wave velocity before the treatment.[59] Low-level sensorineural hearing also improved.[52] many clinical trials have demonstrated that FTIs can induce accumulation of prelamin A and are generally well-tolerated, with adverse effects typically confined to the gastrointestinal tract.[60]

Triple therapy. An extensive clinical trial in 45 patients with HGPS receiving a combination of lonafarnib, pravastatin, and zoledronate therapy found that manifestations in HGPS can be prevented by blocking progerin and geranylgeranylation and farnesylation of prelamin A.[61] Further, zoledronate prevents osteoporosis and pravastatin delays the progression of atherosclerosis.[61,62] About 71.0% met the predetermined outcome criteria and improved in either the carotid artery echodensity and/or the per-patient weight gain.[63,64] Lonafarnib mono and triple therapy in HGPS demonstrated a 1.6-year average increase in survival.[61,62]

Drugs activating autophagy

Rapamycin (Sirolimus). Rapamycin, a blocker of mammalian target of rapamycin, was among the first therapeutic strategies to target progerin turnover.[65] Rapamycin improves the atypical nuclear morphology, autophagic clearance of progerin, delays cellular senescence, and preserves chromatin phenotype in HGPS fibroblasts in culture.[66–69] Like in HGPS, rapamycin, exhibits its promise in a number of neurodegenerative disease models.[66]

Everolimus. Everolimus, a rapamycin analog, increases autophagy to facilitate the cleavage of harmful, insoluble aggregates like progerin,[70] it was also found to improve cell line proliferation and postpone cellular senescence, even in the absence of the traditional HGPS mutation.[70,71] Although lonafarnib monotherapy on these donor-specific phenotypes was more restricted, the combination of lonafarnib and Everolimus treatment had a positive impact on SMC proteins and vasoactivity.[53] Overall, the findings indicate that therapy with these two drugs produced more benefits than either medication used alone. However, determining the therapeutic window requires correct drug dosage.[53]

Sulforaphane. It is an antioxidant found in many cruciferous vegetables and enhances progerin release through autophagy and reverse cellular features of HGPS in vitro.[72] Sulforaphane–Lonafarnib combination had a gradual and synergistic effect on autophagy activation in HGPS fibroblast cultures,[73] even up to toxic levels.[56]

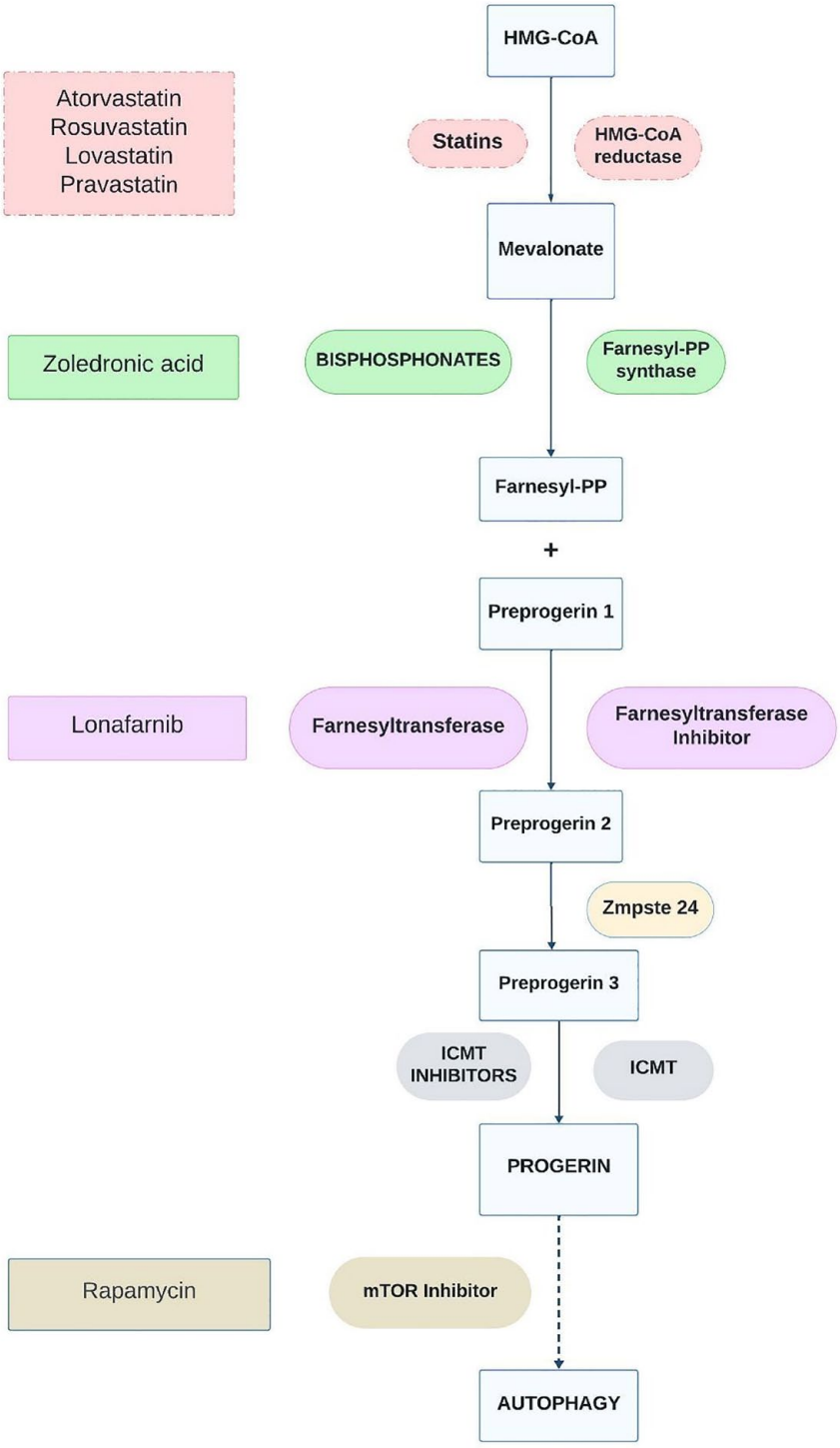

Figure 3. Mechanisms of drug-induced autophagy.

MG132. MG132 is a proteosome inhibitor that can induce progerin clearance in HGPS patients. Proteasome inhibitors have improved progerin clearance mediated by macroautophagy in HGPS patient fibroblasts, IPSC-derived mesenchymal stem cells, and VSMCs. They also

discovered that this compound can indirectly decreased prelamin A increase in the HGPS cellular phenotypes.[74]

Genetic therapy

CRISPR-therapy. Genetic methods such as CRISPR-therapies offer novel strategies to lower production of progerin.[75] HGPS is an ideal candidate for genetic therapy because treating a single-point mutation significantly improves symptoms. Antisense morpholino-based therapy (antisense oligomers that bind to specific nucleotide sequences to inhibit the translation of mRNA) blocking pathogenic *Lmna* splicing significantly increased lifespan in Lmna G609G progeric mouse.[76] A different study reported that antisense oligonucleotide (ASO) boosted lamin C synthesis while decreasing progerin.[77] ASO treatment in mice also reduced progerin expression in tissues indicating possible therapeutic application of ASOs in HGPS.[75] Two recent papers have demonstrated the in vivo benefit of CRISPR-therapies for the first time.[78,79] Therefore, as the technology advances, these therapy will become even more successful.

Adenine base-editing. Adenine base editors (ABEs) convert A·.T base pairs to G·C without causing double-strand DNA breaks, allowing for precise correction of mutations. In progeria, the dominant-negative mutation in the LMNA gene (c.1824 C>T) leads to the production of progerin, a toxic protein. ABE treatment can correct this mutation, restoring normal RNA splicing and reducing progerin levels. In mouse models, ABE treatment significantly improved vascular health, increased lifespan (from 215 to 510 days), and overall vitality, demonstrating its therapeutic potential in HGPS.[80,81]

Remodelin

Remodelin, (a N-acetyltransferase-10 (NAT10) inhibitor, useful in progeria models) causes chromatin compaction while correcting nuclear morphological anomalies, defects in proliferation, and build-up of DNA alterations that are typical of progerin-expressing cells.[81] Several ongoing studies are conducted to track remodelin's impact on gene expression and assess its potential as a treatment approach.

Gut fecal microbiota

The application of fecal microbiota transplantation is among the most intriguing and novel advancements in the treatment of progeria.[75] Bárcena et al. showed intestinal dysbiosis in two progeria mice models and HGPS, which consisted of decreased Verrucomicrobia and increased Proteobacteria and Cyanobacteria. Adding wild-type mice's fecal microbiota to progeria mice increased both lifespan and overall health, demonstrating evidence in favor of microbiome-based HGPS therapy.[75,82]

Supplementation therapy

Vitamin D. Changes in the vitamin D/VDR vitamin D receptors status have a substantial impact on cells and organisms and are linked to a variety of disorders.[83] It exhibits aging traits in VDR knockout mice like HGPS patients do, which includes early hair loss, growth retardation, muscular atrophy, cardiovascular disease, and a shortened lifespan.[84,85] According to Kreienkamp et al., progerin accumulation is linked to lower levels of VDR and DNA repair factors like BRCA1 (breast cancer type 1) and 53BP1 (p53 binding protein 1).[86] The reinstatement of VDR signaling through 1,25-dihydroxy vitamin D3 (1,25D) in HGPS fibroblasts may mitigate pathological characteristics such as nuclear abnormalities, DSB repair defects, and early senescence. Thus, mode of action of vitamin D may involve repairing DNA damage and mitigating replicative stress in progeric cells.[50,87]

Growth hormone treatment. HGPS murine model ($Zmpste24^{-/-}$ mice) shows a marked decrease in plasma IGF-1 (Insulin Like Growth Factor-1). Upon restoring IGF-1 (with recombinant human IGF-1) and growth hormone (GH) levels to the correct ratio, lifespan increased. Further, there was a significant improvement in a number of HGPS phenotypic traits, including alopecia, increased subcutaneous fat, decreased kyphosis, and improved body weight.[88]

Retinoids. Retinoid are currently wait in vivo testing. Retinoic acid responsive elements (L-RARE) in the LMNA gene promoter reduce the expression of the LMNA gene in response to all trans retinoic acid (ATRA) treatments.[89] Combination of ATRA and rapamycin showed synergistic effect

on progerin degradation in HGPS fibroblast cells.[90]

Limitations

HGPS is a rare genetic disorder caused by mutations in the LMNA gene, leading to the production of progerin, which accelerates aging. Symptoms include growth retardation, cardiovascular disease, and early onset of aging-related features. Treatments like FTIs (e.g., Lonafarnib) help improve cardiovascular health and bone strength, while gene therapies such as CRISPR aim to correct the genetic defect. Other therapies, including autophagy activation and GH supplementation, also show potential. Despite promising results, these treatments remain experimental and require further clinical validation to confirm their efficacy.

Conclusion

HGPS is a rare and devastating genetic disorder that accelerates aging and significantly shortens life expectancy. This article has explored the clinical manifestations, genetic basis, and complications of HGPS, highlighting the profound impact of LMNA gene mutations on multiple physiological systems. The core learning from this exploration is the complex interplay of genetic, cellular, and molecular mechanisms that contribute to the premature aging phenotype observed in progeria. Despite the severe limitations imposed by the disease, advances in genetic testing and early diagnosis provide a glimmer of hope for affected individuals and their families.

The future of HGPS treatment lies in ongoing research efforts aimed at targeting the underlying molecular defects. Emerging therapies, such as FTIs and gene editing techniques, show promise in mitigating some of the disease's symptoms and slowing its progression. However, these approaches remain experimental and require further clinical validation. Additionally, the focus on cardiovascular health, given the high mortality associated with heart-related complications, will be crucial in improving patient outcomes.

Despite significant progress in understanding the pathophysiology of HGPS, several limitations remain. The rarity of the condition poses challenges in conducting large-scale clinical trials, and the current treatments only provide symptomatic relief without addressing the root cause of the disease. Moreover, the ethical considerations surrounding gene editing and its long-term effects need careful deliberation. Further research is essential to develop more effective and targeted therapies that can not only extend the lifespan but also enhance the quality of life for individuals with HGPS.

Declaration

Ethics approval and consent to participate

Not applicable as it is a literature review.

Consent for publication

Consent for publication is not required, as this is a review article with no patient data utilized.

Author contributions

Akhil Arun: Conceptualization; Data curation; Methodology; Project administration; Resources; Software; Supervision; Visualization; Writing – original draft; Writing – review & editing.

Athira Rejith Nath: Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Bonny Thankachan: Formal analysis; Methodology; Resources; Visualization; Writing – original draft; Writing – review & editing.

M. K. Unnikrishnan: Formal analysis; Writing – original draft; Writing – review & editing.

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