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REVIEW ARTICLE

Molecular basis and pharmacological approaches for the management of Hutchinson–Gilford Progeria Syndrome

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ABSTRACT

Hutchinson-Gilford progeria syndrome (HGPS), a rare disease that results in what appears to be premature aging, followed by death due to atherosclerosis is caused by the production of a mutant form of prelamin A known as progerin. Mainly two reasons are behind the lamin protein mutation one is “gene expression” and the second one is “mechanical stress’’. The nuclearlamins may also play a role in regulating gene expression, DNA synthesis, and DNA repair, The most common LMNA mutation involves a C-->T transition at nucleotide 1824 (G608G). This substitution results in the activation of a cryptic splice donor site in exon 11, which results in a 150-base pair deletion and a truncated lamin A protein, called progerin. Children with Progeria are born looking healthy. When they are about 10 to 24 months old, features of accelerated aging start to appear. Signs of Progeria may include: Growth failure, Loss of body fat, Loss of hair Skin starts to look aged, Stiffness in the joints Hip dislocation and generalized atherosclerosis (cardio and heart disease) stroke. Atherosclerosis in progeria mainly caused by the decreased levels of HDL than increased levels of LDL. Strategies to increase HDL levels may be useful to treat life threatening symptoms. Stratagies include Physical Therapy (PT), Occupational Therapy (OT) and Hydro therapy along with nutritional therapy as a non-pharmacological approach. The existing pharmacological approaches include Growth hormone treatment, anti-oxidants, Lonafarnib, aspirin and oxygen. These treatments are not completely useful to relief from symptoms. However drugs to improve HDL levels may be useful to treat Atherosclerosis. Zoledronic acid might be improving bone mineral strength in progeria patient.
Keywords: lamin protein, niacin, cholestyramine, gemfibrozil, Zoledronic acid.

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INTRODUCTION

Hutchinson-Gilford progeria syndrome (HGPS) develops accelerated atherosclerosis of the cerebral and coronary arteries. Unlike arteriosclerosis in the general population, however, in progeria, the only lipid abnormality is decreased high-density lipoprotein cholesterol levels. Extensive lipofuscin deposition, a marker for aging, is extensively distributed in patients with HGPS. Affected organs include the kidneys, brain, adrenal glands, liver, testes, and heart [1].

Mutations in the LMNA (Lamin A/C) gene are responsible for this syndrome. Approximately 80% of HGPS cases are caused by a G608 (GGC3GGT) mutation within exon 11 of LMNA, which elicits a deletion of 50 aa near the C terminus of prelamin A. Nuclear alterations affect cell-cycle progression and cell migration and elicit premature senescence. Strikingly, skin biopsy sections from a subject with HGPS showed that the truncated lamin A accumulates primarily in the nuclei of vascular cells. This ending suggests that accumulation of progerin is directly involved in vascular disease in progeria.

BACK GROUND: Mutations in novel transmembrane protein were responsible for X-linked Emery Dreifuss muscular dystrophy (EDmd). Emerin is protein, localized in inner nuclear membrane and absent in patients with Emery Dreifuss muscular dystrophy. Same dystrophy could also be inherited in a non-sex –linked manner. Families with this non sex linked EDmd had mutations in LMNA, the single gene encoding nuclear lamins A and C.

Different motions in the LMNA gene results Dunnigan-type partial lipodystropy, Charcot-Marie-tooth disorder type 2B1, and Hutchinson-Gilford progeria syndrome. There are two reasons behind the lamin protein mutation one is “gene expression” this posits that the correct interaction of the two lamin proteins, A and C, with the nuclear envelope is essential for normal tissue specific expression of certain genes. [2] Thus the basis of these diseases would be a change in gene expression caused by defective protein interactions. The second one is “mechanical stress” hypothesis the mutations in the nuclear lamins-emerin complex thought to weaken the structural integrity of an integrated cytoskeletal network.

ROLE OF LAMIN GENE: The LMNA genes encodes the nuclear A-type lamins, which are type V intermediate filament proteins that localize to the cell nucleus and form the nuclear lamina, a structure that supports the nuclear envelope. They are important in maintaining nuclear stability and organizing nuclear chromatin. The nuclear lamins may also play a role in regulating gene expression, DNA synthesis, and DNA repair.

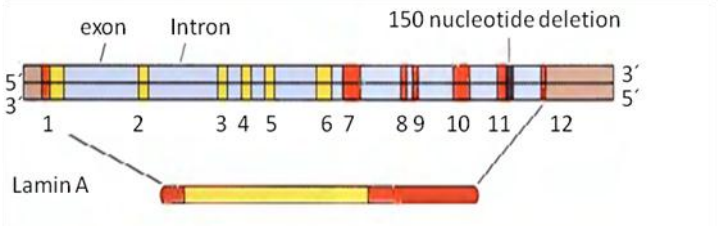

Figure 1

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Molecular and cellular basis: Hutchinson-Gilford progeria syndrome (HGPS) is related to aberrant processing of the nuclear envelope protein lamin A and accumulation of farnesylated prelamin A Autosomal dominant mutations in the LMNA gene, located on band 1q21.1-1q21.3, are responsible for most cases of HGPS. De novo mutations associated with advanced paternal age are responsible for most cases, although maternal transmission of a mutant LMNA gene from an asymptomatic mother who manifested somatic and gonadal mosaicism has also been reported. In addition, autosomal recessive transmission has also been suggested to account for the development of HGPS in several sets of siblings born to unaffected parents.

The most common LMNA mutation involves a C-->T transition at nucleotide 1824 (G608G). This substitution results in the activation of a cryptic splice donor site in exon 11, which results in a 150-base pair deletion and a truncated lamin A protein, called progerin. The abnormal progerin protein acts in a dominant-negative manner to prevent the normal assembly of nuclear lamins into the nuclear lamina. After translation, the mutant preprogerin protein undergoes normal farnesylation of a CAAX tetra peptide motif located at the carboxyterminus. Progerin is thus unable to be cleaved, resulting in a permanently farnesylated form of lamin A. We hypothesized that the retention of the farnesyl group forces progerin to remain embedded in the nuclear membrane and form multimeric complexes with mature wild-type lamin A and other proteins, creating a mislocalized multiprotein complex that alters nuclear structure and function. In support of this hypothesis, mutations in ZMPSTE24 cause a severe form of mandibuloacral dysplasia, which is phenotypically similar to HGPS.

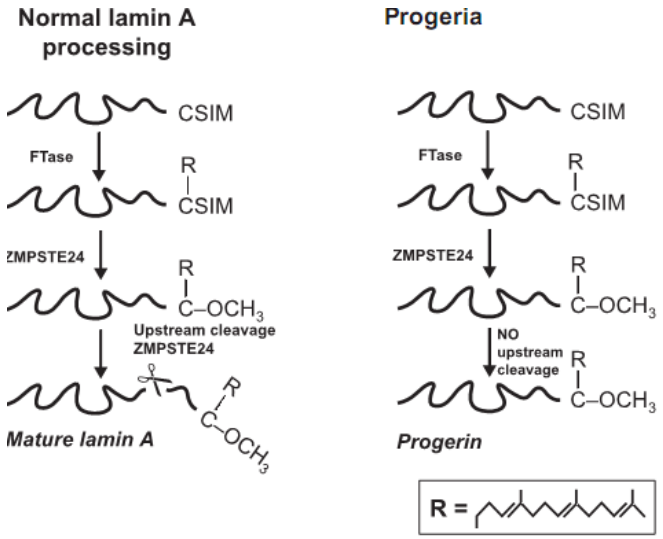

Figure 2

However, the mutant, truncated protein lacks an important post translational processing signal required for cleavage of the preprogerin protein at the carboxyterminus. This cleavage is required for the release of prelamin A from the nuclear membrane, thus allowing its incorporation into the nuclear lamina. The abnormal progerin protein forms insoluble cytoplasmic aggregates.

The cell nuclei from HGPS patients display abnormal nuclear blebbing and aberrant nuclear shapes due to result of the absence of lamin A in the nuclear lamina. Abnormal chromosome segregation and delayed onset and progression of mitosis have also been demonstrated.

The presence of the homozygous missense mutation G1626C (K542N) in LMNA was demonstrated in 5 siblings born to asymptomatic, consanguineous carrier parents. This study confirms that autosomal recessive inheritance of HGPS can also occur.

A transgenic mouse model for HGPS has been created by introducing a splicing defect into intron 9 of the mouse LMNA gene. Transgenic mice displayed many of the features of HGPS, including loss of subcutaneous fat, decreased bone density, growth failure, craniofacial deformities, skeletal abnormalities, and early death. Using microarray analyses, 3 recent studies compared the gene expression profiles of cultured fibroblasts from patients with progeria with those of healthy people of various ages. In general, changes in gene activity detected in older patients correlated with changes in gene activity in progeria patients.

Of the genes expressed differentially in progeria patients, several that help control mitosis were down-regulated. Many genes that control cell division and DNA or RNA synthesis and processing were also shown to be down-regulated in progeria patients; many of these changes are also seen with normal aging. Some of these changes were postulated to lead to genetic instability and a variety of disturbances in gene function.

Changes were also seen in the expression of many genes involved in collagen remodelling and the formation of the extracellular matrix. In general, the changes favoured excess extracellular matrix deposition, which may lead to the characteristic changes seen in the skin and the vasculature in progeria patients. Expression of transforming growth factor-beta, a factor that regulates tissue homeostasis and whose sustained expression is responsible for tissue fibrosis, is highly up-regulated in patients with progeria.

The expression of several transcription factors, including many involved in musculoskeletal development, were also decreased in progeria patients. Expression of MEOX/GAX, a negative regulator of cell proliferation in mesodermal tissue, is elevated almost 30-fold in patients with HGPS, suggesting a contributory role in the development of the musculoskeletal abnormalities seen in HGPS.

HDL levels can be increased by following therapy

Non-pharmacological approach

Raising your HDL levels can be a challenge, because it usually requires lifestyle changes rather than simply taking a pill.

Medical care

There is no proper treatment for HGPS, but the life period of patient will be extended by proper treatment to life threatening symptoms which include cardiac and cerebrovascular arteriosclerosis, arthritis, and stroke.

Progeria need Physical Therapy (PT), Occupational Therapy (OT) and Hydro therapy as often as possible (optimally 2 - 3 times each per week) to ensure maximum range of motion and optimal daily functioning along with improving joint mobility and minimizing symptoms of arthritis throughout their lives.

Nutrition plays a major role to improve the quality of life of effected persons by increasing the protein, mineral content to strengthen the bone mineral density and muscular activity. Monounsaturated fats contain foods like healthy fats olive oil, peanut butter, avocados, etc... Can raise the HDL levels without harming total cholesterol and avoid the artery-clogging by bad cholesterol accumulation. Soluble fiber and pile on the onion which contains chromium can increase HDL cholesterol, avoiding too many processed carbs and Trans fats will protect from accumulation of LDL levels in effected persons.

Pharmacological approach

Although there is no complete cure for progeria, but this pharmacological approaches may improve the life expectancy of progeria patients

Growth hormone treatment:

It has been used to decrease catabolic demands and augment weight gain and linear growth in a small number of patients with progeria.

Antioxidants:

Free radicals plays a major role in pathogenesis of several diseases like arteriosclerosis, ischemic heart disease, ageing, inflammation, diabetes, immunosuppression, neurodegenerative diseases, and many other diseases .Antioxidants having a capability to scavenger the free radicals, should promising results in the management of progeria.

Aspirin:

Atherosclerotic plaques can also suddenly rupture, develop a blood clot on their surface, and completely choke off a portion of heart muscle. This chain of events frequently results in heart attack or sudden death without warning. Low dose of Aspirin is recommended as prophylaxis medicine.

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Lonafarnib:

It is a fernesyl transferase inhibitor currently used as an anticancer drug; these appear to promote the release of mutant prelamin A (preprogerin) from the nuclear membrane, allowing it to be correctly incorporating into the nuclear lamina. This leads to correcting the structure and functions of nuclear defects.

Oxygen:

Cardiac and cerebrovascular arthrosclerosis may affect the functioning of the heart by inadequate oxygen supply. Oxygen will help in life threatening conditions.

My hypothesis:

Arteriosclerosis is a life threatening condition in progeria it is caused by the decreased of HDL levels, and it can be increased by the Hypolipedimic agents.

In patients with reduced HDL –C levels (<35 mg/dl), preliminary studies suggest that statins differ in their effects on HDL-C levels. 80mg of Simvastatin will increase the HDL-C and apoA-1 levels more than a comparable dose of atrovastatin. Provastatin might be elevate the HDL-C levels and also may affect plaque stability in a variety of ways to avoid rupture of plaques.

Cholesterol Level Chart

Blood Cholesterol Level Chart	Desirable (mg/dl)	Borderline (high) (mg/dl)	High Risk (mg/dl)
Total Cholesterol	< 200	200-240	> 240
Triglycerides	< 150	150-500	> 500
Low Density Cholesterol	< 130	130-160	> 240
High Density Cholesterol	> 50	50-35	< 35(progeria)

The blood cholesterol chart shows what your blood cholesterol levels should be and includes low and high cholesterol level measurements.

Niacin appears to be the most effective at raising HDL levels. Niacin is one of the B vitamins. The amount of niacin needed for increasing HDL levels are so high, Niacin enhances the LPL (Lipoprotein lipase) activity, and raises the HDL levels by decreasing the functional clearance of apoA-1 in HDL rather than by enhancing HDL synthesis. Furthermore, "niacin" takes several forms, including nicotinic acid, nicotinamide, and inositol hexaniacinate - and all of these are labelled as "niacin." Unfortunately, only nicotinic acid raises HDL cholesterol, and this drug can be difficult to take because of its propensity to cause flushing, itching and hot flashes. In general, taking niacin to treat cholesterol levels should be supervised by a doctor.

According to the National Cholesterol Education Program (NCEP), niacin (vitamin B3) is an important tool to normalize cholesterol. Several studies have found that this vitamin can increase HDL by 30 percent while lowering total cholesterol by 10 percent to 25 percent.

Fibric acid derivatives (gemfibrozil) enhance the HDL levels by PPAR alpha stimulation of apoA-1 and apoA-ll expression which increases HDL levels.

A three-drug regimen of niacin, cholestyramine, and gemfibrozil has been shown to increase HDL cholesterol substantially, but this drug combination can be particularly difficult to tolerate.

Omega-3: This essential fatty acid, found in fish, fish oil, flaxseed and walnuts, has been found to increase HDL cholesterol.

Zoledronic acid is a bisphosphonate, which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors. It binds to hydroxyapatite and accumulates in bone, thus inhibiting osteoclast migration and maturation. Zoledronic acid an agent used to increase bone mineral density in patient with progeria.

Three drug regimen:

One drug from statins/niacin to increase HDL levels second one zoledronic acid to improve bone mineral density and Lonafarnib a fernesyl transferase inhibitor

CONCLUSION

Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare hereditary disease that affects the skin, musculoskeletal system, and vasculature. HGPS is characterized by signs of premature aging due to production of truncated gene formation of progerin. The existed therapies are not completely use to provide symptomatic treatment. the triple therapy might be useful in progeria that include niacin/statins which can raise the HDL levels and Lonafarnib a fernesyl transferase inhibitor which prevent the formation of truncated gene formation and one zoledronic acid is a bis-phoaphonate to improve bone mineral density to relief from arthritis

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