

The Hutchinson-Gilford Progeria Syndrome and Treatment: Updated Review of the Literature

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Abstract

Original Research Article

Progeria is a rare syndrome, with an estimated incidence of 1 per 250,000 births. It is a fatal, genetically determined disease of childhood characterized by dramatic, premature aging that occurs at about 8 to 10 times the normal rate of aging. Because of this accelerated aging, a child of ten years will have similar respiratory, cardiovascular, and arthritic conditions that a 70-year-old would have. Progeria is the most radical of the ageing illnesses. Although children with progeria has the appearance of premature aging or senility, the term is misleading because reported cases of progeria has not manifested most physical or biochemical aspects of old age. Many children with progeria appear normal at birth and then progressively, and rather rapidly, develop the characteristic features during early childhood. Although first described in the 1880s, only approximately 100 cases of progeria are reported in the international literature. Most of the classical clinical features of progeria as seen 4 or 5 years old age. In a few study there has been a history of maternal illness during pregnancy is main causes of progeria but no specific illness appearing to be significant. The goal of this study was to determine sign and symptoms, investigate mechanisms that cause of HGPS and how to treat the occasional illness of progeria.

Keywords: Progeria, sign and syndrome, causes, mechanism, treatment.

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INTRODUCTION

The first study of progeria to be described in medical literature was that of Hutchinson in 1886, under the title of 'Congenital Absence of Hair and Mammary Glands.' Hastings Gilford recognizing this condition as a clinical entity, described a case of his own and re-described Hutchinson's original case. He introduced the term progeria (post prematurely old). The term "progeria," coined by Gilford in 1904, is used to describe. Children with the appearance of premature aging or senility [1]. The word progeria comes from the Greek words "pro" meaning "before" or "premature", and "gēras" meaning "old age". Progeria is an extremely rare autosomal dominant genetic disorder in which symptoms resembling aspects of aging are manifested at a very early age. Progeria is one of several progeroid syndromes [2-4]. Those born with progeria typically live to their mid-teens to early twenties.[5,6] It is a genetic condition that occurs as a new mutation, and is rarely inherited, as carriers usually do not live to reproduce. Although the term progeria applies strictly speaking to all diseases characterized by premature aging symptoms, and is often used as such, it is often

applied specifically in reference to Hutchinson–Gilford progeria syndrome (HGPS). A prominent physical feature of progeria is marked outward protrusion of the ears (pinna) and absence of ear lobes, yet there is a general consensus observed that hearing in children with progeria is not impaired, at least by clinical examination.[7] According to James W. Hall James C. Denny [8] documented Characteristics of the Progeria Syndrome General (Short stature, Decreased weight for height, Incomplete sexual maturation) Skin (Diminished subcutaneous fat ;Thin, dry, wrinkled skin Prominent superficial veins) Head (Craniofacial disproportionate size, Anterior fontanelle patent, Beaked nose ,Micrognathia, Thin lips, Prominent eyes, Protruding ears, Absent earlobes, "Plucked bird" appearance) Hair(Alopecia (hair loss) Absent eyebrows and eyelashes) Teeth (Dentition delayed and abnormal (crowding) Trunk and Limbs(Pear-shaped thorax ,Short clavicles ;Wide-based, shuffling gate Thin limbs ,Dystrophic finger nails (brittle, yellowish, curved) Radioluscent terminal phalanges Prominent and stiff joints). But Not all characteristics are consistently present The condition is estimated to affect 1 in 4 million newborns with a

total reported cases of 140 worldwide since it's been identified in 1886. This estimate has been based on the number of new children with Progeria which becomes annual born. More publications concerning boys than little girls have appeared, but the proportion of little girls and boys with progeria is in Europe at this moment nearly equal (11: 12) [9] According to the Progeria Research Foundation, as of December 2017, there are worldwilde 144 progeria children. Including 112 children with the classic Hutchinson-Gilford Progeria, who have a progerin producing mutation in the LMNA gene, and 32 Children in the Progeroid Laminopathy category who have a mutation in the Lamin pathway but do not produce progerin. There are 24 children living in Europe (amongst them 3 in Belgium and 1 in the Netherlands). In the past 15 years, children with Progeria have been reported all over the world, including in Algeria, Argentina, Australia, Austria, Belgium, Canada, China, Cuba, England, France, Germany, Israel, Italy, Mexico, Morocco, the Netherlands, Poland, Portugal, Puerto Rico, South Africa, South America, South Korea, Switzerland, Turkey, the US, Venezuela, Vietnam and Yugoslavia. Children with Progeria die of atherosclerosis (heart disease) or stroke at an average age of 12.6 year (with a range of about 8–21 years). Progeria children develop no sex hormones. With Hutchinson-Gilford progeria, death is most often due to arterial atheromatosis and coronary occlusion and generally occurs between 7 and 27 years, with a mean age of 13 .5years [7] Recently, longevity up to 45 years has been reported for three patients [10, 11].

A classical study of progeria is described. The world literature relating to this subject is reviewed and it is concluded that this is typical case to be reported. Approximately as many atypical cases have been described and a separate grouping and naming of these is advocated. The clinical features, diagnosis, pathology, and treatment of progeria are discussed.

Literature study design of sign and symptoms of the Progeria done from different published journals, newspapaers, and google onlines and from other sources are given below.

Signs and Symptoms

We study certain number of paper about progeria and find out symptoms of progeria. Children with progeria usually develop the first symptoms during their first few months of life. The earliest symptoms may include a failure to thrive and a localized scleroderma-like skin condition. As a child ages past infancy, additional conditions become apparent usually

around 18–24 months. Limited growth, full-body alopecia (hair loss), and a distinctive appearance (a small face with a shallow recessed jaw, and a pinched nose) are all characteristics of progeria. Signs and symptoms of this progressive disease tend to become more marked as the child ages. Later, the condition causes wrinkled skin, atherosclerosis, kidney failure, loss of eyesight, and cardiovascular problems. Scleroderma, a hardening and tightening of the skin on trunk and extremities of the body, is prevalent. People diagnosed with this disorder usually have small, fragile bodies, like those of elderly people. The face is usually wrinkled, with a larger head in relation to the body, a narrow face and a beak nose. Prominent scalp veins are noticeable (made more obvious by alopecia), as well as prominent eyes. Musculoskeletal degeneration causes loss of body fat and muscle, stiff joints, hip dislocations, and other symptoms generally absent in the non-elderly population. Individuals usually retain typical mental and motor development [12].

Literature study design of the causes of the Progeria done from different published journals, newspapers, google onlines and from other sources are given below.

Etiology of Progeria

According to Yang SH *et al.*, [13] Hutchinson–Gilford progeria syndrome (HGPS), a progeroid syndrome in children, is caused by mutations in LMNA (the gene for prelamin A and lamin C) that result in the deletion of 50 aa within prelamin A. In normal cells, prelamin A is a “CAAX protein” that is farnesylated and then processed further to generate mature lamin A, which is a structural protein of the nuclear lamina [13]. According to Goldman RD *et al.*, [14] Progeria commonly caused by a point mutation in the lamin A gene that results in a protein lacking 50 aa near the C terminus, denoted LA50. By electron microscopy they show that HGPS is associated with significant changes in nuclear shape, including lobulation of the nuclear envelope, thickening of the nuclear lamina, loss of peripheral heterochromatin, and clustering of nuclear pores .These structural defects worsen as HGPS cells age in culture, and their severity correlates with an apparent increase in LA50. Introduction of LA50 into normal cells by transfection or protein injection induces the same changes. They hypothesize that these alterations in nuclear structure are due to a concentration-dependent dominant-negative effect of LA50, leading to the disruption of lamin-related functions ranging from the maintenance of nuclear shape to regulation of gene expression and DNA replication [14].



Fig-1: Progeria affected patient

Literature study design of the treatment of the Progeria done from different published journals, newspapers, and google onlines and from other sources are given below.

Potential treatment of HGPS

Prior to the HGPS gene discovery, treatments were limited and unsuccessful. For instance, nutritional and growth hormone therapy resulted in only transient improvements in individuals with HGPS [15].

PrelaminA, Isoprenylation and methylation inhibitors

Lonafarnib, Zoledronate/Pravastatin, Monoaminopyrimidines and isoprenylcysteine carboxyl methyltransferase inhibitor:

The aberrant splice event that gives rise to progerin leads to the deletion of the ZMPSTE24 cleavage site normally used to remove the farnesylated carboxy terminus from prelamin A during post translational processing. Consequently, permanently farnesylated progerin remains anchored to the inner nuclear membrane resulting in dominant-negative disruption of the nuclear scaffold upon progerin dimerization with wild-type lamins [16]. Knowledge of these steps predicted that blocking farnesylation using farnesyl transferase inhibitor (FTI) drugs would decrease progerin production and toxicity [17]. Blocking farnesylation of progerin with FTIs restored normal nuclear architecture and resulted in significant reductions in nuclear blebbing both in transiently transfected HeLa, HEK 293, NIH 3T3 cells and human HGPS fibroblasts [18-21]. In transgenic HGPS murine models treated with FTIs, bone mineralization, and weight are improved, lifespan is extended [22, 23] and cardiovascular defects are prevented [24].

In 2007, the above studies led to the initiation of a prospective single-arm clinical trial (ClinicalTrials.gov, NCT00425607), using an FTI called lonafarnib, which was originally developed for the treatment of cancer. A cohort of 25 HGPS patients between 3 and 16 years of age were included in this trial and received lonafarnib for a minimum of 2 years. In 2012, researchers reported that some children with HGPS receiving lonafarnib showed a modest improvement in weight gain.

Carlos Lopez-Otin (Spain) demonstrated the synergistic effect of a combination of Zoledronate (N-BisPhosphonate) and PRAvastatin (statin) (ZOPRA) and their effectiveness to reduce prenylation and rescue HGPS cells defects and the progeroid phenotypes of Zmpste24 mice, including improvement of growth retardation, loss of weight, lipodystrophy, hair loss and bone defects. Likewise, the longevity of these mice was substantially extended [25].

On the other hand, among 21,608 small molecules tested in induced pluripotent stem cell (iPSC) lines derived from HGPS patients, Nissan and colleagues identified several compounds, called monoaminopyrimidines (mono-APs), as new modulators of farnesylation, resulting, in vitro in improved phenotypes associated with HGPS [26].

In addition to isoprenylation, another consequence of defective posttranslational modification to prelamin A in progeria was reported implicating the carboxy methylation that is mediated by isoprenylcysteine carboxyl methyltransferase (ICMT) [27, 28].

Capell et al., PNAS, 2005



Western Blot

Western blot analysis of cellular lysates from human fibroblasts was done as follows. Cells were lysed in buffer containing 10 mM Tris-HCl, pH 7.4, 1% Triton X-100, 0.1% SDS, 0.5% sodium deoxycholate, 1 mM NaVO₃, 150 mM NaCl, 1 mM EDTA, 1 mM PMSF, 1 μM aprotinin, leupeptin, pepstatin. Proteins were loaded in Laemmli sample buffer and subjected to SDS-PAGE followed by immunochemical reactions. Immunoblotted bands were detected by enhanced chemiluminescence (Amersham)

Immunofluorescence

Human fibroblasts grown on coverslips were fixed in paraformaldehyde 4% in PBS at 4°C and post-fixed in methanol at -20°C for 7 min. Samples were incubated with PBS containing 4% BSA to saturate non-specific binding. Incubation with primary antibodies was performed overnight at 4°C, while secondary antibodies were applied for 1 h at room temperature. Slides were mounted with an anti-fade reagent in glycerol and observed with a Nikon E 600 fluorescence microscope equipped with a digital camera. Pictures were elaborated with Photoshop-6 software [29].

Noteworthy Improvements

Weight: One in three children demonstrated a greater than 50 percent increase in annual rate of weight gain, or switched from weight loss to weight gain, because of increased muscle and bone mass.

Bone Structure: Bone rigidity improved to normal levels after FTI treatment.

Cardiovascular: Arterial stiffness, associated with atherosclerosis, decreased by 35 percent. Vessel wall density also improved [16].

Potential therapeutic effects of mTOR inhibitors

Three classes of mTOR inhibitors have been developed: rapamycin/rapalogs that are allosteric mTORC1 inhibitors; ATP-competitive, 'active-site' mTORC1/mTORC2 inhibitors that target the catalytic site of mTOR [30]

Rapamycin

Rapamycin (also known as sirolimus) is a natural compound produced by the bacterium *Streptomyces hygroscopicus* that acts as an allosteric mTORC1 inhibitor [31]. It forms a gain-of-function complex with 12-kDa FKBP12, which binds to the FKBP12/rapamycin-binding (FRB) domain of mTOR only when mTOR is associated with other components of mTORC1. This complex leads to the dissociation of Raptor and loss of contact between mTORC1 and its substrates [32].

The discovery of rapamycin immediately raised great interest in the scientific community for its numerous properties, e.g. as a powerful antibiotic, antiproliferative and immunosuppressant [33]. In 1991, rapamycin was approved by the US Food and Drug Administration (FDA) for the prophylaxis of renal transplant rejection [34] and as a chemotherapeutic agent against renal carcinoma. Moreover, rapamycin has been used to inhibit restenosis after the implantation of stents during coronary angioplasty [35-36].

Rapalogs

The limitations in the solubility and pharmacokinetic properties of rapamycin led to the commercial development of new mTOR inhibitors, such as semi-synthetic rapamycin analogues, named rapalogs or active site inhibitors. Rapalogs have an improved bioavailability when compared with rapamycin, and include CCI-779 (temsirolimus or torisel), RAD001 (everolimus) and AP23573 (ridaforolimus), which have been, and continue to be, tested in a wide range of clinical trials. The orally available RAD001 is more efficacious than rapamycin as it has a higher affinity for FKBP12 [37].

Resveratrol

Resveratrol is a natural polyphenol that shows numerous beneficial effects, acting as an antioxidant, antiinflammatory and anticancer drug. Moreover, it seems to have protective effects against a number of cardiovascular and neurodegenerative diseases [34]. It has been reported that resveratrol can inhibit mTORC1

by blocking the interaction between Deptor and mTOR [38].

Metformin

There is a growing body of evidence that metformin inhibits mTORC1 through a different mechanism, by activating AMPK. AMPK, in turn, blocks mTORC1 [39] regulating its related GTP binding (Rag) GTPases [40] and indirectly activating regulated in development and DNA damage responses 1 (REDD1), a mTOR inhibitor that promotes TSC2 activity [41].

Progerin accumulation is reduced by mevinolin treatment

In the attempt to destabilize progerin, we used mevinolin to obtain defarnesylation. WB analysis of progerin in HGPS fibroblasts subjected to mevinolin treatment. Control fibroblasts were also treated with the farnesyltransferase inhibitor and subjected to Western blot analysis using anti-lamin A/C antibody and anti-pre-lamin A antibody. Beside the expected increase in wild-type pre lamin A caused by mevinolin in all the examined cell lines, a decrease in the amount of progerin was observed in HGPS lysates. The lamin A level was slightly reduced by mevinolin treatment, while amounts of lamin C and emerin were not affected.

Heterochromatin organization in HGPS nuclei is improved by mevinolin/TSA treatment

By Mevinolin treatment of HGPS fibroblasts apparently failed to improve nuclear shape abnormalities. TSA alone did not cause detectable changes in chromatin organization in control or in HGPS cells. Nuclear shape was improved after the combined treatment with mevinolin and TSA.

Ribonucleoprotein levels are reduced in HGPS cells and restored by mevinolin/TSA treatment

We sought to determine if the increased availability of dispersed chromatin could affect the transcriptional activity of HGPS nuclei. The amount of incorporated BrU was reduced in enlarged HGPS nuclei showing major nuclear lamina defects and BrU-containing transcripts were distributed in the nucleus with a non-uniform pattern. After treatment with mevinolin and TSA, BrU incorporation was comparable to controls in most HGPS nuclei, including some enlarged nuclei. Uniform BrU staining was observed in HGPS nuclei after mevinolin/TSA treatment [42].

Consultations and Management

There is no cure for progeria, but occupational and physical therapy can help the child keep moving if their joints are stiff and physical therapy can help the child keep moving if their joints are stiff. Heart health is critical for people with progeria, so the doctor may prescribe statins, nitroglycerin for angina, and routine therapy for congestive heart failure. Eating healthily and getting regular exercise are important. Some

patients may have cardiac surgery to slow the progression of heart disease. Self-care tips may include eating different foods when the lipid, or fat, profile begins to change, and eating small meals regularly to maximize calorie intake. Sun screen is important for protecting the skin, and padding in shoes can help minimize discomfort caused by a lack of fat padding on the body.



Fig-2: Occupational therapy can help to address joint stiffness [43]

Diet: Infants and children with HGPS may experience feeding difficulties and failure to thrive. The use of age-appropriate nutritional supplements is recommended.

Activity: Children with HGPS do not require activity restrictions. With adequate supervision, most children are able to experience a wide range of physical activities.

CONCLUSION

To date, the concepts of a pluriglandular process, an adrenal disturbance, pituitary dwarfism combined with inadequate mesenchymal development, an inborn error of energy metabolism, abnormal metabolism of the connective tissue, and intracellular accumulation of lipofuscin pigment have been proposed to explain progeria. It is suggested that the cardiovascular calcification and scleroderma-like hyaline fibrosis of the corium seen in most cases of progeria, and the elastotic degeneration of the corium in the present case, may be the result of collagenous degeneration. The field of gerontology gained importance relatively late when compared to other areas of research. However, presently a lot of effort is being put in by researchers in this area to delay the normal ageing process and the trauma that follows the common physical, psychological, and social implications associated with it. The inheritance pattern of HGPS is known but it appears mostly as a sporadic disorder. Hence to address it efficiently it will be worthwhile to study the causal cellular and molecular mechanisms that accelerate the ageing process leading to rapid progression of the disease.

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