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Hutchinson-Gilford syndrome: History, causes, phenotype and research advances

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Abstract

Hutchinson-Gilford Progeria Syndrome (HGPS) (Phenotype MIM number 176670) is an autosomal-dominant genetic disorder that leads to accelerated aging and often premature death caused by cardiovascular complications. HGPS is origined by an abnormal Lamin A formation, directly caused by a mutation in exon 11 of the *LMNA gene*. This syndrome is characterized by the presence of aging-associated symptoms, including lack of subcutaneous fat, alopecia, growth retardation, skin pigmentation, joint contractures, osteoporosis, cardiovascular pathologies, and death due to myocardial infarction and strokes in childhood. Aim of this literature review was to document the history, symptomatology and advances in the development of treatment strategies for HGPS. Until now, clinical management of HGPS has been largely based on treatment of the manifestations and prevention of secondary complications, and there is still no cure for the disease. Although copious barriers remain to be overcome before a cure for HGPS can be developed, the increasing understanding of the molecular mechanism of the disease will allow better treatment strategies to be designed in the future.

Keywords: HGPS; Progeria; Premature Aging; Lamin Proteins; *LMNA genes*

1. Introduction

Humans encode four major Lamin proteins: *Lamin B1 (LB1), Lamin B2* (LB2) and Lamins A and C (LA, LC), and are encoded by LMNB1, LMNB2 and *LMNA genes*, respectively. These Lamins are intermediate nuclear filaments, which, in addition to their structural role, are involved in basic nuclear functions such as chromatin organization, DNA replication, transcription and cell cycle progression [1]. Mutations in *LMNA gene* cause several diseases called laminopathies, one of which is Hutchinson-Gilford progeria syndrome (HGPS).

Hutchinson-Gilford syndrome has existed as a recognized clinical condition for more than 100 years [2,3]. It is classified within the group of progerias caused by mutations of *LMNA gene*, and distinguished from others mainly by the age at onset of the first signs and symptoms [4]. The laminopathies associated with this disorder are a heterogeneous group of genetic diseases with a molecular origin based on mutations in LMNA (located at position 1q22). Mutation of this gene produces a mutant LA protein with deletion of 50 amino acids that alters the last cleavage step of pre-lamin A. This truncated LA (pre-lamin A), called progerin, is permanently farnesylated, toxic to cells and shows structural and biochemical alterations [5, 6].

The first case of progeria syndrome was described in 1886 by Jonathan Hutchinson [2]. In his article, the author describes a child who presented an old person appearance; all his limbs were thin, including fingers and nails, which had an extremely thin and fragile appearance and were curved backwards. His height, despite being in puberty, was the

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same as a six-year-old child. His head had an elongated shape, the fontanelle had not closed completely and his face was small; his scalp was extremely thin and hairless. His veins were more noticeable than normal because the skin was delicated and thin. Also, he had basically no adipose or even subcutaneous tissue at all. The mother had become hairless at the age of six and thereafter presented small alopecia areas; after that moment she never had adequate hair growth. Hutchinson was unable to fund research, so he concluded that it was a hereditary pathology and the mother's hair loss at the age of six was related to it. Hutchinson described the case as "a case of congenital absence of hair and mammary glands with an atrophic skin condition and its appendages" [2]. However, years later it would be demonstrated that cases of progeria typically present de novo mutations, meaning that the disease was not transmitted by its progenitors [7].

Ten years later, Gilford [3], at Hutchinson's request, described in greater detail the characteristics of a patient whom he observed for four years. Gilford recognized, at least, some features resembled premature aging (Figure 1). For example, there were signs of quickly development or skin maturation, mucous membranes of the tongue and intestines, hair, nails, and cells of the vascular system; in addition, he had visual hypertrophy. His eyes were long and presented exophthalmos, with superciliary and ciliary madarosis. The nasal cartilage was prominent and the teeth were sparse and irregular. The lower jaw, clavicles and scapulae were small; the chest was flattened with atrophy of the mammary glands. The limbs were thin, with elongations in the epiphyses, mainly in the knees and elbows (Figure 1).

Figure 1 Gilford's (1896) patient at age 7, 12 and 17 years (reprinted from Gilford [3])

Gilford's patient died at 17 years of age from intestinal problems, in addition of problems with his heart valves. Gilford would later report that "his death was as singular as many cases of old people with heart disease" [3]. Gilford proposed the name progeria for this syndrome in 1904.

After these cases, no reports of progeria conditions were found until 1910, when a 15-years-old French girl and a 27-years-old man from the Netherlands were reported; since then, the report of patients from all continents has gradually increased, so that in 1972 there were records of 60 cases around the world [8], and by 2006 the number of cases reported in the literature reached 142 [9]. According to Progeria Research Foundation (PRF), it is estimated that there are between 350 and 450 children (it is approximately 1 case in 20 million) with Hutchinson-Gilford syndrome in the world, and by March 31, 2023, the number of living children and young adults confirmed reached 142 in 51 countries, which means an increase of 63% in the last 10 years.

2. HGPS phenotypical expression

HGPS is a condition mainly characterized by premature and accelerated aging in children. It is an extremely rare condition [10] whose clinical manifestations are evident in the first or second year of life; it includes physical features usually associated with premature aging, causing children to appear elderly. Patients with HGPS have normal fetal development and are born with a healthy appearance; in addition, mentally they are alert and observer children, with

normal intelligence and emotions [11], i.e., they do not present neurological alterations, and for this reason their cognitive and emotional development does not correlate with phenotypic aging [12, 13]. However, between approximately 18 and 24 months of age, they begin to manifest the first histopathological changes, which occur in the form of alterations in connective tissue integrity, an essential organs component and tissues such as bone, muscle, skin, subcutaneous and blood vessels [9].

The most evident signs of HGPS are growth retardation, with below average height and weight; prominent eyes and incomplete eyelid closure; narrow face, small lower jaw, thin lips and curved nose; weight and hair loss, wrinkles and skin pigmentation, stiffness, hip dislocation, generalized atherosclerosis and high-pitched voice, in addition to cardiovascular disease and strokes [10]. Ageing process occurs 5 to 10 times faster than usual, and therefore the patients appear much older than they are [7]. Most children with this syndrome die of heart diseases that affect millions of normal ageing adults [14], for this reason, additional analysis may be necessary; for example, electrocardiogram, dental, vision and audition evaluations. In this context, the median age of death in this pathology is around 13 years, with a range from 8 to 21 years.

2.1. Disorders with similar symptoms

Despite being an extremely rare syndrome, progeria´s manifestations can be confused with other genetic disorders. One of this is Gottron syndrome [15], a very rare condition of premature aging characterized by atrophy of the skin and subcutaneous tissue, but the difference with progeria is that premature aging occurs in the body extremities like hands and feet. Other similar syndrome known as Ehlers-Danlos [16] whose differences with progeria are multiple birthmarks, extremely fragile skin which bruises easily and low-set prominent ears. It has been reported more genetic abnormal conditions with similar characteristics like Wiedemann-Rautenstrauch [17], De Barsy and Hallermann-Streiff [18] syndromes, whose phenotypical manifestations are too close to HGPS clinical manifestations.

3. Genetical alteration leading to HGPS

As mentioned above, mutation of *LMNA gene* results in an abnormal LA protein that modifies the last cleavage step of pre-lamin A. While LA is present both in the periphery and inside the nucleus, progeria is predominantly located in the nuclear periphery [19, 20]. The abnormal (mutant) form of pre-Lamin A disrupts the nuclear envelope and, as a consequence, a cell misdifferentiation occurs or does not occur at all. Tissue restoration and renewal cannot take place and very rapid ageing occurs. Children cells nuclei with progeria are deformed, with structural modifications; molecularly, they have alterations in chromatin organization, which predisposes to double-strand breaks in DNA and inadequate signalling for repair, leading to cell replication arrest and induction of senescence or cell death [21]. Lamin A and C are encoded by the same gene (LMNA) located on chromosome 1, while Lamin B is encoded by the gene (LMNB) located on chromosome 5. The mRNA contains information necessary for the Lamin C synthesis and is formed by transcription of LMNA up to exon 10, while for Lamin A transcription continues up to exon 12. Lamin A is synthesized as a precursor called pre-Lamin A, which has 4 amino acids (CAAX) in its carboxyl-terminal segment, where C is cysteine, A corresponds to an aliphatic amino acid and X to any amino acid. CAAX induces a farnesylation-methylation process, which is essential to give rise to the mature and properly active Lamin A.

The most frequent mutation causing HGPS is a specific mutation at position 1824 in exon 11 of the pre-Lamin A gene, which consists of a cytosine to thymine substitution at the third base of codon 608. This mutation activates a cleavage site in mRNA processing, resulting in the synthesis of a pre-Lamin A variant with loss of 50 amino acids at the carboxyl end (Figure 2). This shorter protein is known as progerin or Lamin AD50, which lacks a cleavage site for the enzyme Zmpte24, and therefore, specifically affects pre-Lamin A maturation into Lamin A, which remains constitutively farnesylated, accumulates in the nucleus and shows structural alterations as well as defects in chromatin organization that develop the symptoms of premature ageing [5, 6].

HGPS originates from the synthesis of Lamin A and progerin, a process that occurs in phases. The first phase that occurs in pre-Lamin A is farnesylation (formation of a farnesyl group, a 15-carbon lipid) to the cysteine thiol group (C) of the CAAX segment by a cytosolic farnesyltransferase (FTase) protein. This protein is directed into the nucleus and recognizes the correct binding site on the nuclear envelope.

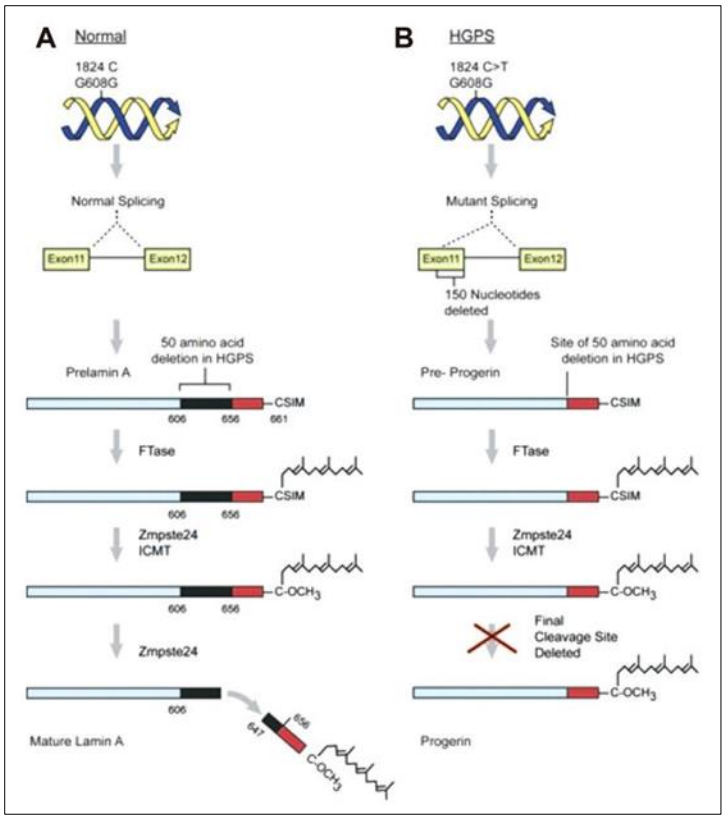

Figure 2 Synthesis of lamin A (left) and progerin (right) causing HGPS. HGPS is caused by a C to T base change at position 1824 of the *LMNA gene* (B). This mutation does not change the encoded amino acid (Glycine) but results in the activation of a cryptic splice site 150 nucleotides upstream of the exon 11-12 splice junction. As a result, progerin lacks the second cleavage found in the pre-Lamin A of the normal (A) population and therefore remains farnesylated (Reprinted from [22]).

In a second phase, the 3-terminal amino acid group (-AAX) is separated from the pre-Lamin, leaving the farnesylated cysteine as the terminal amino acid. This phase takes place in the endoplasmic membrane reticulum by the action of the metalloproteinase Zmpste24. The third phase consists of the methylation of farnesylated cysteine by the isoprenylcysteine carboxyl methyltransferase action, also located in the endoplasmic reticulum. Afterwards, importins translocate pre-lamin A into the nucleus through the nuclear pores, where proteolytic cleavage of pre-lamin occurs by the enzyme Zmpste24. Pre-lamin A is cleaved into two segments: one containing the last 15 amino acids of the pre-lamin A, and which is degraded (including farnesylated and methylated cysteine); the other segment forms the mature lamin A, that fixes to the inner nuclear envelope [23].

In progeria, the shorter abnormal lamin A undergoes the changes of farnesylation, methylation and translocation to the nucleus, but its 15 amino acid terminal segment cannot be cleaved by the enzyme Zmpste24, because the sequences for cleavage and release of the mature protein are absent and, therefore, it remains farnesylated and gives rise to the abnormal protein called progerin (Figure 2) [5].

4. Advances in HGPS management

Hutchinson-Gilford syndrome is one of the most interesting diseases in the history of science. Since the discovery of the gene in 2003, the number of publications has increased considerably to more than 100 scientific articles on HGPS published each year. The Progeria Research Foundation (PRF) alone has a database of 268 scientific publications generated since 2002 as a result of research funded by its support programs. However, there is currently no definitive therapy for HGPS, although some potential strategies have been developed.

One of these strategies is the restoration of the normal phenotype at the cellular level through the use of a morpholino, proposed by Scaffidi and Misteli [24], although this is still at an experimental stage. Other possible strategies include the use of viral vectors to deliver anterograde molecules into blood vessels, such as the aorta and coronary arteries, or selective inhibition by RNA interference techniques [25]. Glynn and Glover [20] raised the scientific community interest

in the farnesylation inhibition of pre-Lamin A, which has been shown to restore the nuclear envelope phenotype in vitro. These authors demonstrated that inhibition of farnesylation prevents the incorporation of progerin into the nuclear envelope, and that just a partial reduction of this incorporation considerably reduces the dominant negative effect of progerin, restoring the normal phenotype. Along the same research line, therapeutic strategies that include messenger RNA interference techniques, and inhibition of the dominant negative influence of abnormal lamin A on the normally polymerisation formed Lamin A, are currently being developed [9].

Lai and Wong [26] conducted a systematic review of the advances in the development of treatment strategies of HGPS from 2010 to 2019. One of the first findings of these authors was that only 14% of the studies report or evaluate the performance of treatment strategies in humans, the rest of the studies have been conducted in mice. In this sense, it is worth noting that although the use of mouse models has streamlined the evaluation of treatment effectiveness, mice remain evolutionarily distant from mammals. Genetic and physiological differences between mice and human patients may limit the transferability of data from preclinical studies to clinical trials [26]. The same authors point out that 94.6% of the studies evaluated have proposed genetic-pharmacological interventions, and few studies (5.4%) have been dedicated to treating HGPS by protein therapy.

Among the different pharmacological treatment alternatives, protein farnesyl-transferase inhibitors (FTIs) are the most widely used therapeutic agents. Among these, the drug lonafarnib is an inhibitor of FTIs, and does not allow the farnesyl group to bind to progerin. This drug has been tested in cell cultures and in animal models with HGPS, reversing the alterations in nuclear structure, as well as improving the cardiac condition of mice treated with FTI when compared to untreated mice [10]. By preventing the abnormal protein (progerin) from binding to the cell's nucleus, the drug achieves the symptoms of progeria to diminish. The use of FTIs has been proposed in combination with the administration of progerin prenylation inhibitors. Examples of these inhibitors include pravastatin [27], zoledronic acid [27] and GGTI-2147 [28]. In addition to the aforementioned FTI-based therapies, Lai and Wong [26] describe other agents used in the pharmacological treatment of HGPS in preclinical trials, including resveratrol, levamisole, ARL67156, MG132, JH4, NRF2-activating agents (oltipraz, CPDT, TAT-14, AI-1), ABT-737, sodium salicylate, β3-AR agonist, spermidine, tauroursodeoxycholic acid (TUDCA) and sodium tetrabasic pyrophosphate decahydrate, all evaluated in mice groups.

Other studies have explored the use of nucleic acid therapy to treat HGPS. Reported strategies for implementing this alternative include prenatal genetic manipulation, anterograde oligonucleotide therapy, and ex vivo genetic manipulation. The implementation of most of these strategies, however, requires the intervention to be performed before birth [29].

More recently, gene-based therapies, such as CRISPR/Cas9, are a promising alternative for the treatment of genetic diseases such as HGPS. Using the CRISPR/Cas9 gene-editing tool, Santiago-Fernandez et al. [30], were able to increase the survival of a group of mice from 127 to 160.5 days, which represented an increase in life expectancy of 26.4%. This experiment was replicated in patients with HGPS, with very optimistic results, although the consequences of editing the original form of lamin A have not been sufficiently investigated. Since these strategies involve prior genetic modification of an individual, they can hardly be implemented in practice. Moreover, due to the ethical issues raised by embryo gene editing, the applicability of these strategies, even to prevent the occurrence of HGPS, may raise ethical and technical conflicts, so their practical usefulness is still in question [26].

5. Conclusions

Hutchinson-Gilford progeria syndrome (HGPS) is an autosomal-dominant genetic disease that leads to accelerated aging and often premature death caused by cardiovascular complications. Until now, clinical management of HGPS has been largely based on treatment of the manifestations and prevention of secondary complications. That is why the progeria treatment and diagnosis must be multidisciplinary involving a geneticist, pediatric odontologist, cardiologist and pediatrician specializing in progeria. Advances in HGPS research have rapidly increased the potential treatment strategies number; however, there is still no cure for the disease. Although numerous barriers have yet to be overcome before a cure for HGPS can be developed, the increasing understanding of the molecular mechanism of the disease will allow better treatment strategies to be devised, so the emergence of a cure might only be a matter of time.

Compliance with ethical standards

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There is no conflict of interests. The author reports no conflicts of interest in this work. By this statement, all authors who consist of Vargas-González Karla Isabella and Lazalde Brissia have no conflict of interest regarding this manuscript publication.

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