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Progeria (Hutchinson–Gilford syndrome) – review of current literature

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ABSTRACT

Hutchinson–Gilford progeria syndrome (HGPS), also known as juvenile progeria, is a genetic disorder associated with abnormalities in the structure and function of nuclear envelope proteins. The disease begins in childhood and causes rapid aging. Affected children usually appear normal at birth and in early infancy, but then grow more slowly than other children and do not gain weight at the expected rate. They develop a distinctive facial appearance, including prominent eyes, a thin nose with a curved tip, thin lips, a small chin and protruding ears. Hutchinson–Gilford progeria syndrome also causes hair loss, premature skin aging, joint abnormalities and loss of fat under the skin. This condition does not affect intellectual development or the development of motor skills such as sitting, standing and walking. It affects 1 in 4 million children worldwide and so far 150 cases have been reported, mostly boys. The average survival is 15 years.

In recent years, there has been significant progress in the understanding of the molecular causes of this rare condition, which contributes to the development of new treatments for this rare condition, to the understanding of the causes of physiological aging in humans and may result in the development of new methods to slow this process.

Keywords: premature aging syndrome; progeria; Hutchinson–Gilford syndrome.

INTRODUCTION

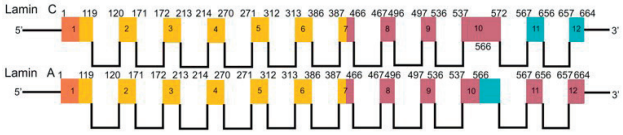
Progeroid syndromes are a group of very rare genetic disorders characterized by clinical features that mimic physiological aging, such as hair loss, short stature, skin tightness, cardiovascular disease and osteoporosis. As a result, they are considered an important source of information for understanding the molecular mechanisms involved in associated with physiological aging.

Progeroid disorders do not show differences in prevalence by gender or ethnicity and appear at an early age, mainly due to defects in nuclear envelope and DNA repair mechanisms. Affected individuals die at a young age, usually as a result of cardiovascular problems and musculoskeletal degeneration. It is believed that the main cause of progeroid syndromes is genetic, associated with specific mutations in 3 classes of DNA repair proteins: protein helicases, nucleotide excision repair proteins, and nuclear envelope proteins [1, 2, 3, 4].

Hutchinson–Gilford progeria syndrome (HGPS) is caused by mutations in the *LMNA* gene encoding lamin A. Lamins are the major components of the nuclear envelope – a structure lining the nucleoplasmic surface of the inner nuclear membrane and forming part of the nuclear envelope. They protect the genetic material from mechanical forces, determining the shape, size and location of the cell nucleus. They influence the proper distribution of pore complexes and connections between the cytoskeleton and the nuclear skeleton, as well as basic processes within the nucleus, such as replication and transcription. It is also believed that lamins may be involved in the physiological process of aging, mitosis, cell differentiation, tumorigenesis processes, apoptosis and influence the course of viral infections [5, 6, 7].

In addition to localization in the nuclear envelope, lamins are also detected inside the nucleus, in the nucleoplasm. Lamins, due to their expression pattern, amino acid sequence, biochemical properties and intracellular localization, can be divided into 2 main classes – lamin A (which also includes lamin C) and lamin B. Lamin A must be processed in the cell before it becomes part of the nuclear envelope. Its initial form, called prelamin A, undergoes a series of complex steps that are necessary for the protein to enter the envelope. Lamin C does not have to undergo this processing before it becomes part of the envelope.

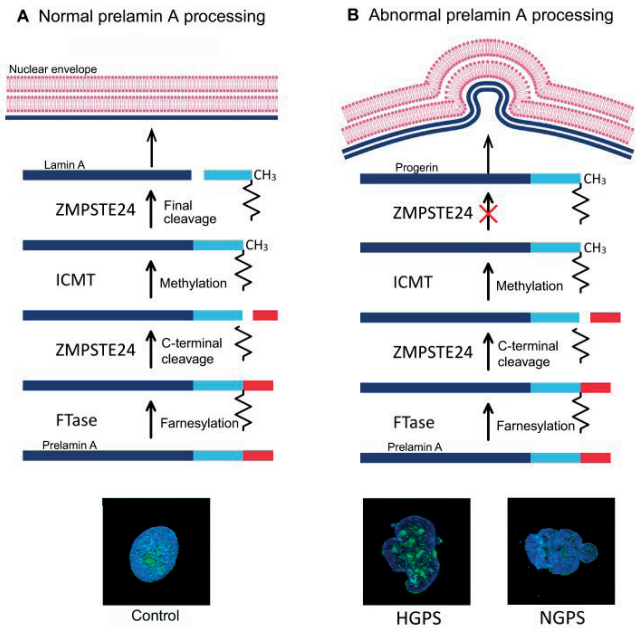
In humans, there are 3 different genes encoding lamins: *LMNA*, *LMNB1* and *LMNB2*, which form mRNAs through alternative splicing (random binding of exons) and undergo post-translational modifications and are the basis for the synthesis of many different variants. Lamins A, C, C2 are formed by alternative splicing processes of the *LMNA* gene [3, 8, 9, 10, 11]. The lamin A/C (*LMNA*) gene contains 12 exons (Fig. 1). Lamin C is encoded by exons 1–9 of this gene and exon 10, while lamin A is formed by alternative splicing, by adding exons 11 and 12 and deleting part of exon 10.



orange – head domain; yellow – central domain; purple – C-terminal domain

FIGURE 1. Schematic mRNA structure of lamin C and lamin A (products of alternative splicing of the *LMNA* gene). The numbers indicate the amino acid residues in the resulting protein, the colors correspond to the domains of the protein. Since lamins A and C are formed by alternative splicing of the *LMNA* gene, they are identical in the sequence of the initial 566 amino acid residues and differ only in the C-terminal fragment [8]

Mutations that cause HGPS result in the production of an abnormal version of the lamin A protein. The altered protein renders the nuclear envelope unstable and gradually damages the nucleus, increasing the likelihood of premature cell death. Figure 2 shows a schematic of the processing of prelamin A in normal cells, leading to the synthesis of mature lamin A and normal nuclear envelope architecture (Fig. 2A), and in the cell with the G608G mutation in the gene encoding prelamin causing HGPS (Fig. 2B). In the cell with the mutation, alternative splicing is activated resulting in the deletion of 50 amino acids above the C-terminus. In the deleted fragment of the polypeptide chain is the cleavage site used by zinc metallopeptidase STE24 (ZMPSTE24) so no mature lamin A is formed. This fact leads to the accumulation of a toxic form of lamin A derivative called progerin. The disturbance in the energy of the nuclear envelope caused by the lack of lamin A leads to the formation of bulges of the membrane, known as nuclear blebbing. An image of human HGPS fibroblasts compared to control cells is shown in Figure 2. Progerin remains permanently attached to the inner nuclear membrane and this contributes to the HGPS phenotype [8, 9, 10, 11].



FTase – farnesyltransferase; ICMT – isoprenylcysteincarboxylmethyltransferase; HGPS – Hutchinson–Gilford progeria syndrome
Cell nuclei were stained – fluorescent dye (DAPI – blue color), A/C lamins – green color)

FIGURE 2. Prelamin processing: A) physiological process; B) pathological process and shape of cell nuclei in normal and pathological cases of Hutchinson–Gilford progeria syndrome [3]

EPIDEMIOLOGY

Hutchinson–Gilford progeria syndrome is an extremely rare genetic disorder, with a reported prevalence of 1 in 8 million births. However, when unreported or misdiagnosed cases are taken into account, the estimated number of births with the disease is 1 in 4 million [12]. According to the Progeria Research Foundation database [13], which is the main online database about the disease, there are an estimated 350–400 children living with progeria worldwide, but only 132 of them had been identified as of October 1, 2015. The identified cases come from 46 different countries, suggesting that the disease affects all ethnic groups and genders equally and has no reported geographical clusters [14].

On April 16, 2003, a press conference was held at the National Press Club in Washington, D.C., announcing the discovery of the Progeria gene. The discovery made it possible to begin research on the role of gene mutations in atherosclerosis and on variants of the *LMNA* gene that could extend life instead of shortening it. Reports by 2 groups of researchers from France and the US about the cause of HGPS have been published in leading scientific journals [15, 16, 17, 18, 19]. They show that children with progeria live an average of 13 years with death caused by diseases associated with increased atherosclerosis, namely stroke or myocardial infarction. Eriksson et al. conducted research on cells obtained from 23 people with HGPS. The researchers detected in the patients a gene mutation (conversion of a single cytosine nucleotide to a thymine nucleotide) in the LMNA gene on chromosome 1. They proved that the defective protein, lamin A, synthesized on the matrix of the mutated DNA fragment, does not fulfill the assigned role of nuclear membrane stabilizer. Studies of the genome of parents of children with progeria have not revealed somatic mutations, which means that gene mutation occurs at the germline level [16]. Thus, progeria is not a hereditary disease in the traditional sense of the word since it is not possible for parents to pass on the allele with the defective gene to their offspring, as those affected do not live to procreate.

CLINICAL SYMPTOMS

Hutchinson–Gilford progeria syndrome is characterized by clinical features that usually develop in childhood and resemble some features of accelerated aging [19, 20, 21, 22, 23, 24, 25, 26, 27, 28]. Children with HGPS appear normal at birth and in early infancy and have a normal body weight. The only worrisome changes that may appear on the child's body are possible pimples and redness. The first noticeable symptoms of the disease begin to appear between 10–24 months of age when the toddler's body begins to age at a very rapid pace. These include muscle tension, stiffness and thinning of the skin, lack of normal weight gain, low growth, hair loss, including eyelashes and eyebrows. A typical feature is the loss of subcutaneous adipose tissue, beginning in the extremities and extending to the chest and face, making children with progeria look much older than their peers. Poor weight gain and loss of subcutaneous fat causes weight and height to fall below the third percentile for age. There are disproportions in skull structure – the cerebrocranium is disproportionately large in relation to the facial skull, and the forehead is very prominent and high. Characteristic facial features include macrocephaly with the undersized mandible (micrognathia), narrow nasal dorsum and tip, narrow upper and lower

lip cinnabar, small lips, sunken cheeks, and bulging eyes. The patient suffers from nocturnal lagophthalmos – the inability to close the eyes completely during sleep.

The skin is thin, sagging and almost translucent, covered with wrinkles, with abnormal pigmentation characteristic of older people. Veins are visible on the scalp. Fingernails and toenails become dystrophic. In addition, the lower abdomen and proximal calves may show dimples or irregular small bulges.

In children with progeria, tooth development is slow and abnormal (delayed eruption and delayed loss of deciduous teeth, partial eruption of secondary teeth, crowding of teeth). In about 50% of affected individuals, a short, thick lingual frenulum is observed, which limits the mobility of the tongue. The narrow airway and rigid laryngeal structures result in a characteristic high-pitched tone of voice.

In addition, loss of fatty tissue can cause ulcers on the front surface of the shin and on the feet. People with HGPS are particularly susceptible to hip dislocation due to progressive hip bone malformation, which can be accompanied by sterile necrosis of the hip joint (bone necrosis). Sterile necrosis can cause hip pain and is visible on X-ray. Coxa valga causes a wide, slouching gait. Additional bone changes include osteolysis of the distal phalanges, short clavicles with distal resorption, pear-shaped rib cage and moderately low bone density in relation to age. Fractures are not more commonly reported in people with HGPS. Extramedullary calcifications occur in 40% of cases with unknown clinical significance. Progressive joint stiffness due to joint ligament strain and osteoarthritis occurs with variable severity.

In patients there is a lack of clear features of sexual maturation manifested by the absence of pubic and axillary hair and the absence of breast enlargement in girls. Women reach Tanner stage 1 (78%) or 2 (22%) at puberty, and about 60% of women experience their first menstrual period [24]. Fertility has not been described. Serum leptin concentrations in serum are below the detection limit. Insulin resistance is present in about 50% of individuals, without overt development of diabetes.

Progeria affects not only the outward appearance of patients – their internal organs also become prematurely damaged and "worn out". The most severe lesions affect the blood vessels and the heart. Due to the quickly progressing atherosclerosis, patients often develop hypertension in just a few years. Individuals with HGPS develop severe atherosclerosis, usually without apparent abnormalities in lipid profiles [25, 26]. Serum cholesterol, low-density lipoprotein and triacylglycerol concentrations are not elevated, and high-density lipoprotein concentrations may decrease with age. Diastolic dysfunction is an early cardiac abnormality, usually detected above the age of 5 by tissue Doppler echocardiography [27]. Further symptoms of cardiovascular deterioration include ventricular hypertrophy associated with hypertension Myocardial ventricular hypertrophy, which is a complication associated with hypertension or aortic valve regurgitation. Mitral and aortic valve abnormalities, including calcification, stenosis and regurgitation, usually develop in the second decade of life. In addition to hypertension, patients also develop other diseases typical of old age, such as osteoporosis, rheumatic diseases and heart failure. Nosebleeds and headaches occur, and low-frequency conductive hearing loss can occur. Remarkably, despite all the aging features, progeria patients do not show an increased incidence of neurodegenerative diseases or cancer.

It is worth noting that the mental development of patients with progeria is normal. In intelligence tests, they achieve age-appropriate results, and sometimes even show a higher level of intelligence than their peers. They are oriented to their own condition and behave in an age-appropriate manner, eagerly interacting with the environment and forming friendships. However, making friends is often hampered by the unique appearance of the patients – their peers are often afraid of them or do not recognize peers in them, but older people.

The life expectancy of children with progeria is about 15 years. Death is usually caused by complications resulting from severe arteriosclerosis, including myocardial infarction due to atherosclerosis of the coronary arteries and stroke due to the atherosclerosis of cerebral arteries or critical narrowing of the internal carotid arteries.

DIAGNOSTICS

Physical examination of the child is the first essential element in the diagnosis of progeria. If, on physical examination, the child shows clinical signs characteristic of HGPS, he or she should be referred for in-depth genetic diagnosis. The identification of a defective variant of the *LMNA* gene in 2003, responsible for the development of progeria, allowed the development of a molecular test that can detect the pathogenic gene variant.

The diagnosis of HGPS with a classical or non-classical genotype is established in a proband with characteristic clinical features, along with the identification of a heterozygous pathogenic variant in *LMNA*, which causes the production of the abnormal lamin A protein progerin. Individuals with the classical HGPS genotype are heterozygous for the pathogenic variant c.1824C>T (~90% of individuals with HGPS). Individuals with the non-classical HGPS genotype have the characteristic clinical features of HGPS and are heterozygous for another pathogenic *LMNA* variant in exon 11 or intron 11 that causes progerin production (~10% of individuals with HGPS) [15].

Finally, it is worth mentioning the Progeria Research Foundation established in 1999, which deals with children affected by progeria, with the goal of discovering new treatments for progeria and related disorders resulting from premature aging [13].

TREATMENT AND PREVENTION

The cause of progeria has recently been identified, but work is still underway to understand it. A major achievement was the discovery of the progeria gene in 2003 [15]. The first ever clinical drug trials began in 2007 [15, 16]. One possible treatment for progeria is farnesyltransferase inhibitors (FTIs) [29,

30, 31, 32, 33]. These are currently used to treat cancer, but researchers believe they can reverse the nuclear abnormalities believed to cause progeria [34]. Studies in mice with progeria-like symptoms suggest that FTIs may alleviate the symptoms of the disease [35]. In September 2012, the results of the first clinical trial of treating children with progeria using FTI were published. Findings showed significant improvements in bone structure, weight gain and cardiovascular system [36]. In 2014, another study showed that an FTI known as lonafarnib could extend life by an average of 1.6 years [37, 38]. Lonafarnib (Zokinvy™) is an oral active FTI initially developed by Merck & Co. as an experimental drug in oncology. In progeria, lonafarnib inhibits farnesyltransferase, preventing farnesylation and subsequent accumulation of progerin and progerin-like proteins in the nucleus and cell cytoskeleton. In November 2020, lonafarnib received its first approval in the US in order to reduce the risk of mortality in HGPS and is currently under regulatory review in the European Union. Unfortunately, progeria still remains an incurable disease, and current treatment consists of alleviating or delaying some of the symptoms of the disease.

The doctor may suggest medications and changes in the sick child's diet to lower cholesterol or prevent blood clots. A regular diet with frequent small meals is recommended. Low-dose aspirin (2–3 mg/kg body weight) is recommended in the prevention of cardiovascular complications and stroke. Antisclerosis therapy is a routine treatment for congestive heart failure. Growth hormone is used to help gain height and weight.

Physical and occupational therapy plays an equally important role in the treatment of progeria, which can help a child with degenerative joint changes. Routine physiotherapy and occupational therapy, active stretching and strengthening exercises, and hydrotherapy are recommended. Physical activity should be self-limited. Physical activities with a large group of peers should be avoided due to the risk of injury. Playing on trampolines and inflatable houses is not advisable due to the risk of hip dislocation. Cushioned shoes or insoles are recommended, which can alleviate the discomfort caused by the lack of body fat and encourage the child to play and be active. Also, while outdoors, the child should use sunscreen with a broad spectrum with an sun protection factor of at least 15. It should be reapplied every 2 h or longer if the child sweats or swims.

Monitoring the patient's health status involves performing follow-up diagnostic tests. At least once a year, the patient should be ordered tests to assess cardiovascular fitness – electrocardiography, echocardiography, ultrasound of the carotid arteries. An magnetic resonance imaging (MRI) of the brain with evaluation of possible ischemic foci in the brain should be performed once a year. In assessing the condition of the hip and knee joints, a classic X-ray is recommended, while assessment of bone mineral density requires densitometry.

Laboratory tests consist of control of lipid metabolism (plasma lipid profile), carbohydrate metabolism (fasting glucose and insulin levels) and determination of the coagulation system parameters.

SUMMARY

Confirming the critical biological links between progeria, heart disease and aging is very important over developing methods to manage the symptoms of the disease. Better understanding of progeria may offer new insights into the aging process.

It appears that the same molecular mechanisms that are responsible for premature cellular aging in patients with Hutchinson–Gilford progeria also contribute to chronological cellular aging. Aging is a complex process involving the entire body, including the skin. Learning about the molecular mechanisms of broadly defined progeria may result in the acquisition of a peptide whose action will help reduce the causes of intrinsic skin aging.

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