Historical Review and Prospects for the Treatment of Hutchison-Gilford Syndrome

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ABSTRACT

Progeria is a syndrome of premature aging, characterized by changes in the skin and internal organs. The term "progeria" was introduced by Dr. Gilford in 1904, who studied the clinical and morphological features of this pathology [1]. It occurs in both children and adults. Children have Hutchinson-Gilford Syndrome (SHG), adults have Werner Syndrome (WS).

The disease is hereditary and is transmitted in an autosomal recessive manner, so isolated cases of brothers and sisters with progeria are explained by the fact that the parents were quite close relatives, for example, cousins, and the disease was the result of incestor. However, other causes of the disease are also called, for example: diencephalic-pituitary insufficiency; secondary damage to several glands of the endocrine system; is the result of one of the manifestations of other endocrine hereditary diseases.

Keywords:

Children's progeria - Hutchinson-Gilford syndrome, was first described by the English physician Jonathan Hutchinson in 1886 in a six-year-old boy with atrophy of the skin and its appendages. Later, his compatriot Hastings Gilford (Hastings Gilford) studied the clinical and morphological features of this disease. Adult - Werner's syndrome was first described by German medical student Otto Werner in 1904. He observed four siblings aged 31 to 40 with a combination of short stature, cataracts, scleroderma, and early graying of the hair [2].

Hutchinson-Gilford syndrome is caused by an autosomal dominant mutation in the LMNA gene, which synthesizes the Lamin A protein. Werner's syndrome is caused by an autosomal recessive mutation in the WRN gene, encoding the WRN protein of the same name. Till date, more than 80 different mutations of the WRN gene have been described, most of which are point missense mutations [3].

The prevalence in childhood is one in 4 million, and in adults it is 1 in 20 million. The highest prevalence is observed in Japan at 1:100,000 [4]. In most cases, progeria occurs sporadically; there are also cases of progeria in siblings, including consanguineous marriages, which indicates the possibility of an autosomal recessive type of inheritance [5].

Premature aging is a feature of other rare progeroid syndromes.

Werner's syndrome is premature aging after puberty with thinning hair and the development of conditions characteristic of old age (eg, cataracts, diabetes mellitus, osteoporosis, atherosclerosis). Rothmund-Thomson syndrome is characterized by premature aging with increased susceptibility to cancer. Both are caused by a gene mutation leading to a defect in the RecQ DNA helicase, which is normally involved in DNA repair [6].

Cockayne syndrome is an autosomal recessive disorder caused by a mutation in the ERCC8 gene, which plays an important role in DNA excision repair. Clinical symptoms include severe growth failure, cachexia, retinopathy, hypertension, renal failure, skin photosensitivity, and mental retardation [7].

Neonatal progeroid syndrome (Wiedemann-Rauthenstrauch syndrome) is a recessive inherited syndrome of aging leading to death before the age of 2 years. It is considered extremely unfavorable, since a unified treatment strategy has not yet been developed and life expectancy does not exceed 27 years, with an average of 13 years. The most common causes of death are exhaustion, myocardial infarction, malignant neoplasms, intercurrent diseases - accidentally joined and complicate the course of progeria itself. Individuals with adult progeria usually live to 40–50 years of age [8].

The study of mouse models of progeria led to the discovery of an amazing opportunity to slow down not only progeria, but also aging. Four transcription factors have been discovered that block the formation of lamin-A. These factors were first obtained by the Japanese scientist Shinya Yamanaka in 2006, after whom they are also sometimes referred to as "Yamanaka factors". When these four proteins are introduced into the cell in the form of a “cassette”, the production of lamin-A in the cell is suppressed, and the somatic cell itself not only stops aging, but also turns into an induced pluripotent stem cell. Induced stem cells, like embryonic stem cells (embryonic stem cells were discovered in 1998), can turn into any somatic cells, in particular, “repair” tissue damaged by both progeria and normal aging [9].

A number of clinical cases of this disease are described in the literature. Tiffany Wedekind from Columbus, Ohio. Doctors considered this case unique, as she lived to be 41 years old. The woman weighed only 26 kilograms with a height of 135 centimeters and suffered from hair loss, tooth loss and heart problems. Despite her health condition, Tiffany practiced yoga and ran a cleaning company. In 2012, her 39-year-old brother Chad died of an illness. Then the woman's parents were worried that their daughter would also overtake an early death. “I knew that I was different from the rest, but it didn’t bother me. I liked my individuality,” said the American. “But when my brother passed away, I suddenly realized that this could be the end of my life.”

According to Tiffany, the parents decided to look into the causes of their children's illness when Chad's health became critical. Then the family members were examined and found out that Tiffany and her mother Linda (Linda Wedekind) suffer from progeria. Doctors were surprised that Linda did not show symptoms of the disease in her entire life. Doctors concluded that Tiffany's mother can also be recognized as one of the oldest carriers of Hutchinson-Gilford syndrome [10].

Leon Botha is a South African artist, musician and DJ. Also known as one of the few people who survived to the age of 26 with progeria. Leon was diagnosed with progeria at the age of four. Botha successfully underwent heart surgery in 2005 to prevent heart attacks due to progeria-related atherosclerosis. Leon Botha died on June 5, 2011 from progeria just one day after his 26th birthday [11].

Sam Burns was the only child of pediatricians Scott Burns and Leslie Gordon. The couple found out about their son's diagnosis when he was not yet two years old. Burns' parents and his maternal aunt, Audrey Gordon, founded the Progeria Research Foundation, an organization devoted to studying and educating people about progeria. In 2003, doctors, whose group included Burns's parents, isolated the gene responsible for progeria. However, no cure has yet been found.

In 2013, Burns was the subject of a documentary called Life from Sam's Point of View. The film was nominated for an Oscar for Best Documentary. Burns commented on the painting's purpose as follows: "I'm not showing you my life so that you feel sorry for me. You do not need to feel sorry for me, because I just want you to get to know me better, to know about my life” [12].

Hayley Leanne Okins was born in 1997 in South Cambridgeshire to Mark and Carrie Okins. As a result of congenital progeria, her body aged eight times faster than normal. Okins has been

involved in spreading the word and raising awareness about Progeria. She has made many television appearances in English, American and Australian programs. Oakins has been involved in an experimental treatment for progeria in the US that has had some positive effects. She passed away on April 2, 2015. She was 17 years old, but physically her body was similar to that of a woman over 100 years old [13].

Ontalametse Falatse died in 2017, shortly after celebrating her 18th birthday. In 2009, doctors diagnosed progeria. She was predicted that she would not live longer than 13 years. However, Ontalametse, contrary to expectations, celebrated her 18th birthday with South African President Jacob Zuma in Pretoria before passing away two months later [14].

There is currently no cure for Hutchinson-Gilford Progeria Syndrome (HGS), although several therapeutic strategies have been developed to improve the clinical features and life expectancy of patients with HGS. The first strategy aims to block prelamin A farnesylation with a farnesyl transferase inhibitor (FTI, lonafarnib). Lonafarnib prevents the formation of nuclear vesicles and reduces the binding of progeria to the nuclear membrane, which leads to the restoration of normal nuclear morphology. In 2007, lonafarnib FTI was tested in the first clinical trial in patients with Chronic subdural hematoma. The treatment increased median individual survival by 1.6 years, increased body weight, reduced skeletal rigidity, and improved bone mineral density in patients with Chronic subdural Hematoma. However, lonafarnib also leads to side effects such as diarrhea, nausea, and anorexia. Lonafarnib was approved by the US Food and Drug Administration (FDA) in 2020. Although FTI improves some of the symptoms of Chronic subdural Hematoma, it is not a cure. Therefore, further attempts to repair cellular defects in Chronic subdural Hematoma are needed [15].

The synergistic effect of two drugs with different mechanisms of action may be more effective than that of a single drug, allowing much lower doses to be used and thus possibly reducing the risk of side effects. Indeed, high concentrations of JAK inhibitors (Janus kinases), a group of proteins that play an important role in initiating responses for several major families of cytokine receptors (in immunology, these proteins are markers of the inflammatory process), can reduce the number of neutrophils and block immune responses. One study evaluated the effects of MnTBAP-Mn(III)tetrakis(4-benzoic acid)porphyrin chloride, a cell-permeable superoxide dismutase (SOD) mimetic, and a peroxynitrite scavenger, alone and in combination with Bar-baricitinib, on Chronic subdural Hematoma fibroblasts. The aim of the study was to answer the question whether MnTBAP can restore mitochondrial function in Subchorionic Hematoma cells and whether Bar can act synergistically to improve cellular homeostasis and morphology in Subchorionic Hematoma cells. MnTBAP/Bar has been shown to partially restore mitochondrial function in Chronic subdural Hematoma fibroblasts, making MnTBAP/Bar a potential combination treatment for CSH.

Combination treatment with MnTBAP/Bar improves the growth rate of Chronic subdural Hematoma fibroblasts and reduces replicative aging to a level similar to either drug alone. MnTBAP and Bar are two drugs that act on different signaling pathways in cells. MnTBAP is a cell-permeating SOD-Superoxide dismutase mimetic and peroxynitrite scavenger, while Bar is a small molecule that specifically and reversibly inhibits JAK1 and JAK2 (Janus kinase 1,2 inhibitors). Therefore, Bar blocks the activation of the STAT family of transcription factors that control the expression of genes involved in inflammation, cell proliferation, and cell growth.

Control and SCH cells were treated with sham or increasing concentrations of MnTBAP (2.5–50μm) for 4 days with medium change every other day. On the 4th day, the number of cells was determined. Experiments showed that the dose of 5μm MnTBAP was the optimal concentration, as it maintained the growth rate of control cells and CCH cells and did not cause toxicity compared to analogues treated with shams [15].

Conclusion. Despite all that is known about CSH and significant advances in the understanding of

the disease, much remains to be learned. Enormous progress has been made over the past decade in understanding this disease. The next decade represents a further path to develop these discoveries and advance new therapeutic strategies to help these patients. As research continues, SCH continues to uncover the under-appreciated mysteries of aging. Patients with CHS experience systemic accelerated aging and die in adolescence from myocardial infarction or stroke due to severe atherosclerosis.

Progeria expression increases with age in normal individuals, suggesting a role for it in physiological aging.

Current therapies are aimed at reducing the toxicity of progeria by lowering its levels or by directly affecting disturbed cellular processes. The best treatment for patients with CSH remains a matter of intense debate. Understanding the full range of functional effects of various drugs will allow us to find strategies in the coming years that will improve the dramatic phenotypes characteristic of CSH while reducing toxicity. Proposed treatments for progeria target several mechanisms that cause the disease. To date, there has been limited improvement in disease phenotypes in mouse models of CSH with the various treatments tested, and this is even more true in patients with CSH. It could be assumed that the age of patients in clinical trials could determine the outcome of treatment, but according to a clinical trial using lonafarnib, it was found that there was no relationship between age at the time of treatment and treatment outcome measures. At the same time, it should be noted that, given the limited number of participants, it is difficult to give a statistically reliable assessment of the results obtained. As research progresses, it becomes clear that focusing the pathophysiology of progeria on one level is likely to be insufficient to significantly alleviate the symptoms and alter the normal course of such a multi-organ devastating disease. Thus, the treatment of CSH associated with progeria accumulation may be based on a combination of several approaches, including a decrease in the expression of key proteins, an increase in the degradation of mutated genes, and the use of multivariate personalized treatment.

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