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Short Communication

Pediatric Premature Aging Diseases

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Abstract

Pediatric premature aging disease are rarely found in pediatric population. The most known disease is Hutchinson Gilford Progeria (HGPS), but other very rare preaging diseases were described in detail. This brief report focuses on the most important preaging diseases in childhood, focus on pathogenesis and possible future therapeutical options.

Keywords: Hutchinson gilford progeria; Pathogenesis; Genetic disorder; Premature aging diseases.

Brief Report

Progeria is a very rare genetic disorder in which affected children appear to age at a time-lapse rate. Progeria is not progeria. The most often form, Hutchinson Gilford Progeria (HGPS), is a disease caused by a defect in a structural protein in the matrix of the cell nucleus [1,2,3,5,8,9,11,16,20,21,27,31]. This protein, lamin A, forms a scaffold of fibrils inside the nucleus that is not only important for structural stability, but also has important roles in the reading of genetic information, organization of the transcription complex and in nuclear division. In most children with progeria, there is an exchange of the last base in codon 608 of the lamin A/C gene (LMNA) [1,2,3,5,8,9,11,16,20,21,27,31].

This change does not result in an amino acid exchange but generates a new splice site. This new splice site results in the excision of 150 nucleotides of the coding sequence, so that the resulting Lamin A protein is 50 amino acids shorter than the normal protein. Children affected by progeria have the mutation on only one allele; it does not occur in the parents [1,2,3,5,8,9,11,16,20,21,27,31]. Lamin A forms dimers, which then assemble into larger fibrils. It is likely that the incorporation of the protein generated by the defective transcript results in disruption of the overall complex. Those affected age five to ten times faster than people without this disease. The most frequent causes of death are heart attacks and strokes, which already occur in childhood or adolescence[1,2,3,5,8,9,11,16,20,21,27,31].

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However, many phenomena of normal aging do not occur in children with HGPS; for example, the risk of tumors is not relevantly increased, and neurodegenerative diseases such as Alzheimer's disease do not occur more frequently [1,2,3,5,8,9,11,16,20,21,27,31]. HGPS is thus not an exact copy of normal aging. Life expectancy is fourteen years [1,2,3,5,8,9,11,16,20,21,27,31]. The prevalence is estimated at 1:4,000,000 [1,2,3,5,8,9,11,16,20,21,27,31].

Approximately 200-250 children are thought to be living with HGPS worldwide [1,2,3,5,8,9,11,16,20,21,27,31]. One cause of progeria is a point mutation c.794 A→G (N265S), chromosome 1 gene locus p34.2, in the ZMPSTE24 gene, which encodes the enzyme CAAX-prenyl protease or zinc metallopeptidase-Ste-24 homolog. This is essential for the formation of the structural protein lamin A, which is an important component of the inner nuclear membrane. Mutant ZMPSTE24 cannot necessarily separate prelamin A at amino acid 647 to eliminate prenylation and produce the finished 646 AA (amino acid)-long lamin A.

However, in the majority of cases of HGPS, a mutation of the prelamin gene in codon 608 on chromosome 1 gene locus q23 itself occurs, changing the trinucleotide GGC to GGT. Although this codes for the same amino acid, the altered base sequence inserts a splice site (5'AC) in the corresponding pre-mRNA. This faulty splicing results in a prelamin RNA that is 150 bases shorter and a lamin A that is 50 AA shorter, also known as progerin. The interface for processing to lamin A is missing, and ZMPSTE24 cannot cut prelamin A. A too-short prenylated lamin remains. Less commonly, a change of codon 608 to AGT or a mutation of codon 145 is found. To date, approximately 250 cases of HGPS have been identified.

Another very rare pediatric premature aging syndrome is known. Nestor-Guillermo Progeria Syndrome is a progeroid laminopathy with autosomal- recessive inheritance, an incidence of 1:1000000 [4,17,19]. 4 variants do exist (4,17,19). Onset is after 2 years of age, alive a long lifespan [4,17,19]. A LMNA/ ZMPSTE24 mutation is responsible for the extremely rare disease in childhood [4,17,19]. Werner Syndrome is a defect in the WRN gene on short arm of chromosome 8 (p12-p11.2), a chromosome break syndrome [24,26]. A full expression after age 30 is present [24,26]. Depending upon such factors, treatment methods may include Genetic counseling is recommended [24,26]. The three RecQ-helicase-mutant disorders, which induce premature aging in children are Werner-,Bloom and Cockayne syndrome. Mutations in the BLM gene (15q26.1), which encodes the DNA helicase, are the cause of Bloom syndrome [10,15,22,24]. An autosomal recessive inheritance is found [10,15,22,24]. Treatment is symptomatic. Higher caloric density in the form of special formulas and foods can promote weight gain and growth. Although growth hormone treatment can improve length growth, many physicians advise against its use because early onset of cancer has been observed in some treated children [10,15,22,24].

Standard antibiotic regimens are used to treat infections. For low serum levels of immunoglobulins and repeated infections, treatment with intravenous or subcutaneous immunoglobulins was given to some patients. Skin protection, including covering exposed skin and using a broad-spectrum sunscreen with a SPF of at least 30, is critical to reduce sun-sensitive rash [10,15,22,24]. Recommendations for medical surveillance of individuals with Bloom syndrome have been

published, including recommendations for cancer screening. Due to patient hypersensitivity to chemotherapy, reduced dosage and/or duration of therapy is recommended, usually starting at 50% of the weight-based dosage. Cockayne syndrome type A and B do exist and differ in different mutations of ERCC6 and ERCC 8 gene [18]. Cockayne syndrome type A shows mutation in ERCC 8-, Cockayne Syndrome type B in ERCC 6 gene [18]. Only 120 cases are described worldwide to date [18]. Congenital restrictive dermopathy is induced by mutations of the ZMPSTE24 gene [23]. 80 cases to date are described in world literature [23]. The disease is described as a form of congenital lethal arthrogryposis multiplex [23]. Hallermann-Streiff syndrome is another rare pediatric premature aging syndrome [6,7]. 150 cases to date were described [6,7]. First record of this disorder was made by Aubry in 1893 [6,7]. More than 150 cases of Hallermann Streiff syndrome have been reported till date [6,7]. The genetic cause in unknown, it is found sporadically [6,7]. First efforts to genetically treat Hutchinson Gilford progeria in mice was performed successfully [27-30]. Overall, Hutchinson Gilford progeria is well known in the field of premature aging syndromes in a small population of children, classified as laminopathic progeria. But the field of premature pediatric aging syndromes are wider, induced most often by sporadic point mutations, chromosome break syndromes or RecQ-helicase-mutant disease progression. In conclusion, all these diseases are absolute rarities in the field of pediatrics, but a clearer classification should be recommended in the future.

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