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Progeria: A brief review

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Abstract

Progeria, also known as Hutchinson Gilford Progeria Syndrome, was initially reported by Jonathan Hutchinson in 1886 and further described by Hastings Gilford in 1904. It is anatypical genetic disorder, usually not inherited, characterised by extreme short stature, low body weight, early loss of hair, lipodystrophy, scleroderma, decreased joint mobility, oesteolysis, facial features that resemble aged person (premature aging) and accelerated cardiovascular disease. In this, the patients are mentally alert and attentive with normal intelligence and emotions. It is mostly caused by a de novo point mutation in the lamin A gene that activates a cryptic slice donor site, producing a truncated mutant protein termed "progerin''. Clinical manifestations are evident by the first or second year of life and include the physical characteristics usually associated with the elderly. In the past, doctors had to base their solely on physical symptoms but today ProgeriaResearch Foundation has establishedProgeria cell and tissue banks to assist in further research and diagnostic process. Treatment usually includes aspirin which helps prevent the atherothrombotic events, stroke and heart attacks by hindering platelet aggregation. Vitamin and fluoride supplementation are also routine therapeutic recommendations for Progeria patients.

Key-Words: Progeria, Hutchinson Gilford Progeria Syndrome, HGPS, Premature Aging, LMNA

Introduction

ProgeriaSyndrome is a rare genetic disorder characterized by dramatic premature aging and accelerated cardiovascular disease.[1] The term Progeriais derived from the Greek word 'pro' meaning early and 'geros' meaning old age.[2] Progeria was first described in 1886 by Jonathan Hutchinson and also described independently in 1897 by Hastings Gilford. Hence, the condition was later re-named after them as Hutchinson Gilford ProgeriaSyndrome (HGPS).[3]

Classical HGPS is usually caused by a sporadic mutation taking place during the early stages of embryo development. It is almost never passed on from affected parent to child, as affected children rarely live long enough to have children themselves (very few children with Progeria live past the teen years to be 21).[4] HGPS has a very low incidence and most of these children hardly survive before they step into adolescent age. The maximum survival chances are not more than 13 years; although many have been known to live upto their late teens and early twenties and rare individuals may even reach their forties. [1]Early death is usually caused due cardiovascular expectancy of a child diagnosed with Progeria. Scientists are particularly interested in Progeria because it might reveal clues about the normal process of aging. [2]

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Epidemiology

HGPS is a very rare disorder prevalent in 1 in 4-8 million newborns.It affects both sexes equally and all races. Currently, there are an estimated 200-250 children living with Progeria worldwide at any one time.[5]

There have been only two known cases in which it became evident that a healthy person can carry the LMNA mutation that causes progeria. These carriers were identified because they passed it on to their children. One family from India has five children with progeria, although this is not a classical HGPS; they were the subject of a 2005 Bodyshock documentary entitled The 80 Year Old Children, while another from Belgium has two. [6]

Symptoms

HGPS develops a characteristic facial appearance including prominent eyes, a thin nose with a beaked tip, thin lips, a small chin, and protruding ears. It also causes hair loss (alopecia), aged-looking skin, joint abnormalities, and a loss of fat under the skin (subcutaneous fat).[7] This condition does not disrupt intellectual development or the development of motor skills such as sitting, standing, and walking.[8] Over the course of the disease, the child's heart and circulatory abnormalities become progressively worse and usually account for the most significant health. Such children usually die from cardiovascular problems as for

example atherosclerosis, but some have died due to convulsions or various types of malnutrition as well.[9,10] Symptoms of HGPS based on various parameters of health are enlisted below:

Growth
- Short stature and stunted growth
- Weight distinctly low for height
- Head disproportionately large for face

Body fat
- Diminished subcutaneous fat
- Prominent scalp veins
- **Skin/Teeth**
- Generalized alopecia
- Delayed and crowded dentition

Skeletal system
- Distal phalangeal osteolysis
- Delayed anterior fontanelle closure
- Pear-shaped thorax
- Micrognathia
- Short, dystrophic clavicles
- "Horse-riding" stance
- Coxavalga
- Thin limbs
- Tightened joint ligaments

CVS
- Severe, progressive atherosclerosiswith widely variable age of clinical manifestationresulting in myocardial infarction and stroke

Other
- Prominent eyes
- Lagophthalmos
- Wide-based, shuffling gait
- Failure to complete secondary sexualdevelopment
- The following features are also seen frequently in HGPS patients:

Body fat
- Prominent superficial veins

Skin
- Thin, taut, dry, wrinkled skin that is brown-spotted in various areas
- "Sclerodermatous" skin over lower abdomen and proximal thighs, in which irregular bumps reflect underlying lipodystrophy
- Loss of eyebrows and sometimeseyelashes
- Dystrophic nails

Skeletal system
- Persistently patent anteriorfontanel

Other
- Pinched nose, beaked nasal tip
- Faint nasolabial cyanosis
- Thin lips
- Protruding ears; lack of ear lobes
- Thin, high-pitched voice

Individuals having most of these features areconsidered to have the classic HGPS. Individuals with either more orless severe feature are considered to have atypical progeria.[1,5,7-9]

Causes

There is a connection between length of telomeresand rapidity of aging. The repeating sequences ofTTAGGG that cap each chromosome (known as atelomere) decreases in length after each replication.Once the telomere reaches a critical length the cellcan no longer divide, becoming senescent.[11] Progeriapatients were found to have excessively shorttelomeres. Shortening of telomeres is associatedwith aging skin, blood, muscle, central nervoussystem, and cardiovascular cells. Progeria patientsusually die from heart disease, heart attacks, orstroke around the age of 13. While Progeria patientsshow abnormal body phenotype, mentally, Progeriapatients are normal and can interact properly. Unlike most other "accelerated aging diseases"progeria is not caused by defective DNA repair.Progeria is an autosomal recessive disease.[12] Thismeans that an individual carrying a mutation in asingle gene does not show any sort of symptoms. Ithas been discovered that ninety percent of theprogeria-affected children have a mutation inposition 1824 of the LMNA gene, replacing cytosine with thymine, creating anunustable form of the protein Lamin A. Lamin A is part of the building blocks of the nuclear envelope. It either develops during cell division in a newly conceived child or in the gametes of one of the parents. However, the real and exact reasons have not yet been identified. Progeria occurs intermittently. It is generally not seen in siblings of affected children. However, in rare cases, it can so happen, that more than one child in a family can succumb to progeria. Nuclear lamin A is a protein scaffold on the inner edge of the nucleus that helps organize nuclear processes such as RNA and DNA synthesis. Prelamin A contains a CAAX box at the C terminus of the protein (where C is a cysteine and A is any aliphatic amino acids). This ensures that the cysteine is farnesylated and allows prelamin A to bind membranes, specifically the nuclear membrane. After prelamin A has been localized to the cell nuclear membrane, the C-terminal amino acids, including the farnesylated cysteine, are cleaved offby a specific protease. The resulting protein is now lamin A, is no longer membrane-bound, and carries out functions inside the nucleus.[13]

In HGPS, the recognition site that the enzyme requires for cleavage of prelamin A to lamin A ismutated. Lamin A cannot be produced, and prelamin A builds up on the nuclear membrane, causing a characteristic

nuclear blebbing.[14] This results in the premature aging symptoms of progeria.

A study that compared HGPS patient cells with the skin cells from LMNA young and elderly human subjects found similar defects in the HGPS and elderly cells, including down-regulation of certain nuclear proteins, increased DNA damage, and demethylation of histone, leading to reduced heterochromatin[15]. Nematodes over their lifespan show progressive lamin changes comparable to HGPS in all cells but neurons and gametes[16]. These studies suggest that laminA defects contribute to normal aging.

LMNA gene

A-type and B-type lamins (Type V intermediatefilaments) are the main components of thenuclear lamina, the innermost layer of the nuclear envelope. The nuclear lamina in mammalian cell is a thin (20–50 nm) protein meshwork that interacts with various proteins and chromatin and isessential for maintaining the structural integrityof the nuclear envelope, the protective barrierbetween the cytoplasm and nucleus.[17] The A-type lamins are encoded by LMNA (MIM150330), which spans 57.6 kb of genomic DNA.By alternative splicing of its 12 exons, four proteins are created: two minor products: laminAD10 and lamin C2; two major products: laminA and lamin C. Lamin A is coded by exons1–12 and lamin C is derived from LMNA by use ofan alternative splice site in intron 10. Thus, laminC differs at the C-terminal from lamin A, since itlacks the final part of exon 10, as well as exons 11and 12. Lamin A, a 664 amino acid proteinwith a molecular weight of 70 kDa, is normallysynthesized as a precursor molecule, called prelaminA. It contains a CAAX-box motif at theC-terminus, which is subject to farnesylation.After farnesylation, an internal proteolytic cleavageoccurs, removing the last 18 coding aminoacids to generate mature lamin A.[18] Lamin C isslightly smaller with a length of 574amino acidsand a weight of 65 kDa. Together, the two proteinsform heterodimers through their roddomains, to create the filamentous structuresfound in the nuclear lamina.[19]

Diagnosis: Molecular diagnostics

As most cases of HGPS appear to be due to a de novo mutation in the same codon (G608G), screening for this mutation is certainly theoretically feasible, especially with the decreasing cost of genomic DNA analysis. However, due to the sporadic nature of the phenotype, predictive screening is not practical at present, since there is no way to determine which children are at risk. Furthermore, the benefit is limited, considering that there is no present treatment for progeria. For the parents of a previously affected child, parental somatic mosaicism is a theoretical possibility. Concerns about the recurrence of HGPS in future pregnancies for such individuals might now be addressed through genetic testing. LMNA testing may also be valuable in making a molecular diagnosis in an individual affected with a suggestive phenotype, that is, to determine whether their disease was 'classical' HGPS or atypical progeroid. As mentioned above, a precise molecular diagnosis may be important, as future therapies may depend upon knowing the genetic basis of the phenotype.[20]

Clinical Diagnosis

Actually there is no clinically approved test todiagnose progeria up to date. Until 2003, in order todiagnose Progeria, doctors observed phenotype i.e.,physical symptoms, such as skin changes and afailure to gain weight, which were not fully apparentuntil a child's first or second year of life, as well as x-raysof patients and urinary hyaluronic acid testingbut had no definitive test.

Urinary hyaluronic acid testing

Chemical testsmay reveal elevated levels of chemical hyaluronicacid in the urine as well as certain fatty compounds,and reduced levels of certain primary antioxidantenzymes in the blood. This may also increaselikelihood of death, as one cause of aging is believed to be a buildup of oxidants in the blood over time.Althoughurinary hyaluronic acid has been reported to beincreased in most children with HGPS themeasurement is now regarded as unreliable and isnot recommended for diagnosis.[21] Now- a-days, with the discovery of the mutated Lamin A gene, blood samples and a skin biopsy taken from patients can be evaluated for presence of the mutated gene, this gives an definitive diagnosis. Additionally,the Progeria Research Foundation has set up a newDiagnostic Program whose first goal is to establish aProgeria cell and tissue bank to assist in furtherresearch. Scientists are exploring possibilities ofusing existing drugs to block or reduce production ofthe abnormal Lamin A protein in children withProgeria.Today the only treatmentfor Progeria patients is administering a low dose ofaspirin throughout their lives. Aspirin may helpprevent atherothrombotic events, stroke and heartattacks by hindering platelet aggregation. Currentlythere is no cure for the disease. [22]

Prenatal Testing

Prenatal diagnosis for HGPS ispossible by analysis of DNA extracted from fetalcells obtained by amniocentesis usually performed atabout 15-18 weeks'gestation or chorionic villussampling (CVS) at about 10-12 weeks' gestation. Thedisease-causing

allele of an affected family membermust be identified before prenatal testing. [23]

Note: (1) Because HGPS has thus far not been reported to recur in families, prenatal testing would only be performed because of the (unlikely) possibility of germlinemosaicism in one of the parents. (2) Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Pre implantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member for laboratories offering PGD.[23]

Treatment

To date, no effective therapy is available for HGPS. But, careful monitoring for cardiovascular and cerebrovascular events is essential. The use of low-dose aspirin is recommended as prophylaxis against cardiovascular and cerebrovascular atherosclerotic disease.

- Physical and occupational therapy can help to maintain physical activity and an active lifestyle. The use of hydrotherapy may be particularly effective in improving joint mobility and minimizing symptoms of arthritis.
- Infants with HGPS may exhibit poor feeding. Provision of adequate nutritional intake may require placement of a gastrostomy tube for supplemental enteral feeding. In older children, the daily consumption of high-energy supplements is recommended, along with careful monitoring of growth and nutrition.
- The use of growth hormone has been used to decrease catabolic demands and augment weight gain and linear growth in a small number of patients with progeria.[24]
- In vitro studies suggest a possible role for the use of FarnesylTransferaseInhibitors (FTI) in HGPS. FTIs appear to promote the release of the mutant prelaminA (preprogerin) from the nuclear membrane, allowing it to be correctly incorporated into the nuclear lamina, thus correcting the structural and functional nuclear defects.
- In vivo studies using FTIs in transgenic mouse models have demonstrated encouraging results with regards to prevention of the cardiovascular complications seen in progeria as well asreversal of the cutaneous manifestations and overall improvement in many of the phenotypic features of progeria, including increased longevity.[25]
- Preliminary in vitro studies usingtransfection of modified oligonucleotidesthat target the cryptic splice site thatoccurs in patients with the common 1824C→T mutation have producedencouraging results. By eliminating theproduction of the mutant LMNA mRNAand protein, normal nuclear morphologyis restored, with resultant normalizationof heterochromatin structure and gene expression. These nascent studiesprovide early support for therationalization of genetic therapy forHGPS patients.[26]

Complications

Death due to cardiovascular abnormalities occurs in approximately 75% of HGPS patients. Other causes of death mentioned in the literature include stroke, marasmus, inanition, seizures, and accidental head trauma.

Conclusion

Hutchinson GilfordProgeria Syndrome is a rare disease. Skin, bone, and cardiovascular structures are primarily involved. Skin and bone abnormalities account largely for a premature aged appearance, and cardiovascular changes account largely for death. Research has shown that progeria does not unequivocally parallel the normal aging process at an accelerated rate and that a connective tissue defect may possibly explain the syndrome. Elevated levels of a ground substance component, hyaluronic acid, which normally increases with advancing age, have been detected, but whether this elevation is of sole causal significance remains to be shown. Further inquiry is warranted to explain the fundamental determinants of this disorder fully.

Despite being described in as early as 1886, it was not until this last decade that the precise cause of HGPS has been elucidated. Gene discovery paved the way for a greater understanding of HGPS, exploration of treatment options, as well as insight into the potential role of prelamin A in the general aging process.

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