

An Overview : Progeria

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Summary

Progeria is an extremely rare genetic disorder, characterized by rapid ageing, from childhood. In other words, it is normal human ageing, but happening at thrice the speed in children. The classic type of Progeria (there are different forms) is Hutchinson-Gilford Progeria Syndrome (HGPS). The earliest symptoms include failure to thrive and a localized scleroderma-like skin condition. As a child ages past infancy, additional conditions become apparent. Limited growth, alopecia, and a distinctive appearance (small face and jaw, pinched nose) are all characteristics of progeria. Most treatment focuses on reducing complications (such as cardiovascular disease) with heart bypass surgery or low-dose aspirin.

Keywords:- Progeria , Hutchinson-Gilford Progeria Syndrome, A Child rare disease

Introduction

Progeria is an extremely rare genetic disorder, characterized by rapid ageing, from childhood. In other words, it is normal human ageing, but happening at thrice the speed in children. Almost all the children afflicted with progeria have a mutation or biological chance on the gene that encodes Lamin A, a protein. Hutchinson-Gilford Progeria Syndrome (“Progeria”, or “HGPS”) is a rare, fatal genetic condition characterized by an appearance of accelerated aging in children. Its name is derived from the Greek and means "prematurely old." While there are different forms of Progeria^{*}, the classic type is Hutchinson-Gilford Progeria Syndrome, which was named after the doctors who first described it in England; in 1886 by Dr. Jonathan Hutchinson and in 1897 by Dr. Hastings

Gilford. Progeria is a rare genetic condition that produces rapid aging in children. The word Progeria comes from the Greek progeros meaning 'prematurely old'. The Greek word pro means 'before', while the word geras means 'old age'. HGPS (Hutchinson-Gilford Progeria Syndrome) or Progeria is an extremely rare, fatal genetic condition. Progeria affects children and gives them an appearance of accelerated aging. The classic type of Progeria (there are different forms) is Hutchinson-Gilford Progeria Syndrome (HGPS). Progeria was first described in an academic journal by Dr. Jonathan Hutchinson in 1886, and Dr. Hastings Gilford in 1897 - both in England. According to Hayley's Page "At present there are 53 known cases of Progeria around the world and only 2 in the UK". There is a reported incidence of Progeria of approximately 1 in every 4 to 8 million newborns. Both boys and girls run an equal risk of having Progeria. Progeria appears to affect children of all races equally. Over the last 15 years the following countries have had reported cases - Algeria, Argentina, Australia, Austria, Canada, China, Cuba, England, France, Germany, Israel, Italy, Mexico, the Netherlands, Poland, Puerto Rico, South Africa, South America, South Korea, Switzerland, Turkey, the US, Venezuela, Vietnam and Yugoslavia. In this disease the aging process of the body accelerates much faster than what it does in normal humans. This process of aging gallops to about seven times the normal rate. Because of this accelerated aging, a child of ten years would have a look of 70 years old. He or she may also have similar respiratory, cardiovascular, and arthritic conditions that a 70-year-old would have. There is no cure for this disease.⁽¹⁾ The exact cause is unknown, but it is believed due to a single abnormal (mutant) gene. Normally for each gene there are two copies, one from each parent. Progeria is considered to be the result of a dominant mutation because the gene in question has one normal copy and one abnormal copy, as opposed to a recessive mutation in which both copies are abnormal. Because neither parent carries or expresses the mutation, each case is believed to represent a sporadic new mutation which happens at the time of conception.⁽³⁶⁾ Progeria, or Hutchinson Gilford Progeria syndrome, is an extremely rare, fatal genetic condition of childhood with striking features resembling premature aging. The word Progeria is derived from the Greek meaning "prematurely old". Hutchinson Gilford Progeria accelerates the process of aging to about eight times the normal rate. Because of this accelerated aging, a child with Hutchinson Gilford Progeria that is ten years old will have similar respiratory, cardiovascular, and arthritic conditions of that of an eighty year old.⁽²⁾

Hutchinson Gilford Progeria has a reported incidence of about 1 in 8 million newborns. It affects both sexes equally and all races. In the past 15 years, children with Progeria have been reported all over the world, including in Algeria, Argentina, Australia, Austria, Canada, China, Cuba, England, France, Germany, Israel, Italy, Mexico, the Netherlands, Poland, Puerto Rico, South Africa, South America, South Korea, Switzerland, Turkey, the US, Venezuela, Vietnam, and Yugoslavia. Hutchinson Gilford Progeria is one of the world's rarest diseases.⁽³⁾ There are only about 40 known cases throughout the world to this date. There has been only about 100 reported cases since the first diagnosis by Jonathan Hutchinson in 1886 and Hastings Gilford in 1904. Progeria is a debilitating, rare illness and genetic disorder with just 45 odd cases in the world. The disease which infects one in four lakh people, is present in India too. Children with Progeria usually have a normal appearance in early infancy. At about 9-24 months of age, children with Progeria begin to experience profound growth delays, resulting in short stature and low weight.

These children also develop a distinctive facial appearance characterized by a disproportionately small face in comparison to the head, an undeveloped jaw, and malformation and crowding of the teeth, abnormally prominent eyes, a small nose and a subtle blueness around the mouth. By the second year of life, children with Progeria lose their hair from the scalp,⁽³³⁾⁽³⁴⁾⁽³⁵⁾ lose their eyebrows and eye lashes. Small, downy, white or blonde hairs may replace the scalp hair. Hutchinson Gilford Progeria is extremely difficult to diagnose in newborns, but certain suspicious findings may be present at birth, such as unusually taut, shiny, hardened skin over the buttocks, upper legs and lower abdomen, and bluish discoloration of the skin around the mouth. Profound, progressive growth retardation usually becomes evident by approximately 9-24 months of age. According to reports in the medical literature, affected children who are 10 years of age typically have a height of that of an average 3 year old.⁽⁴⁾

Although the time of onset of more definitive symptoms varies from case to case, generally by the end of the first year there is noticeable growth retardation and the appearance of physical features commonly associated with Hutchinson Gilford Progeria. Progeria is a life limiting disease that results in the Progeria children dying of heart disease and other ageing related problems at an average age of 13, with a range of about 8-21 years of age.⁽⁵⁾ Progeria affects between 1 in 8 million (approx.) children, with a total reported incidence of just over 100 in the century since it's been identified. There are currently between 30 and 40 known cases worldwide of Progeria. Children from all races and cultures from around the world have been affected.⁽⁶⁾ Because of the lack of a specific laboratory test at this time, the diagnosis must be based on the physical appearance of the individual. The diagnosis is usually made in the first or second year of life when skin changes and failure to gain weight become apparent. Scientists are particularly interested in progeria because it might reveal clues about the normal process of aging.^{[6][7][8]} Progeria was first described in 1886 by Jonathan Hutchinson.^[9] It was also described independently in 1897 by Hastings Gilford.^[10] The condition was later named Hutchinson-Gilford Progeria Syndrome (HGPS). Progeria has a reported incidence of about 1 in 4 - 8 million newborns. It affects both sexes equally and all races. In the past 15 years, children with Progeria have been reported all over the world, including in Algeria, Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Columbia, Cuba, Denmark, Dominican Republic, Egypt, England, France, Germany, India, Ireland, Israel, Italy, Japan, Libya, Mexico, Morocco, Netherlands, Pakistan, Peru, Philippines, Poland, Portugal, Puerto Rico, Romania, South Africa, South Korea, Spain, Sweden, Switzerland, Turkey, United States, Venezuela, Vietnam, and Yugoslavia.⁽⁷⁾

Signs and symptoms

The earliest symptoms include failure to thrive and a localized scleroderma-like skin condition. As a child ages past infancy, additional conditions become apparent. Limited growth, alopecia, and a distinctive appearance (small face and jaw, pinched nose) are all characteristics of progeria. People diagnosed with this disorder usually have small, fragile bodies, like those of elderly people. Later, the condition causes wrinkled skin, atherosclerosis, kidney failure, loss of eyesight, hair loss, and cardiovascular problems. It is not transferred by the offspring.⁽⁸⁾

Children with Progeria are born looking healthy. When they are about 10 to 24 months old, features of accelerated aging start to appear. Signs of Progeria may include:

- Growth failure
- Loss of body fat
- Loss of hair
- Skin starts to look aged
- Stiffness in the joints
- Hip dislocation
- Generalized atherosclerosis (cardio and heart disease)
- Stroke
- Growth failure during the first year of life
- Narrow, shrunken or wrinkled face
- Baldness
- Loss of eyebrows and eyelashes
- Short stature
- Large head for size of face (macrocephaly)
- Open soft spot (fontanelle)
- Small jaw (micrognathia)
- Dry, scaly, thin skin
- Limited range of motion
- Teeth - delayed or absent formation
- Dwarfism.
- Small face and jaw in relation to size of head.
- Delayed tooth formation.
- Wrinkled and aged-looking skin.
- Stiffness of joints. Hip dislocation.
- Baldness
- Pinched nose.
- Mental growth is equivalent to other children of the same age.
- Most children with Progeria live no longer than their early teenage years, though one or two have lived to be as old as 20 or 21.
- Generalized atherosclerosis and cardiovascular problems.
- Narrow, wrinkled or shrunken face
 - Baldness
 - Dry, scaly, thin skin
 - Relatively larger looking size of head, compared to the body
 - Greying hair
 - Loss of eyebrows or eye lashes
 - No teeth, delayed or absence of formation
- Children suffering from this disease tend to have remarkably similar appearance in spite of being of different racial background.
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Although they may come from varying ethnic backgrounds, children with Progeria have a surprisingly similar appearance. Progeria patients generally die between the ages of 8 and 21 - with the average age being 13. Although they are born looking healthy, children with Progeria begin to display many characteristics of accelerated aging at around 18-24 months of age. Progeria signs include growth failure, loss of body fat and hair, aged-looking skin, stiffness of joints, hip dislocation, generalized

atherosclerosis, cardiovascular (heart) disease and stroke. The children have a remarkably similar appearance, despite differing ethnic backgrounds. Children with Progeria die of atherosclerosis (heart disease) at an average age of thirteen years (with a range of about 8 – 21 years).⁽⁹⁾

A child with this condition show signs of symptoms usually around 18–24 months. After being born a healthy looking baby, their height and weight suddenly fall below average for their age. Individuals generally retain normal mental and motor development. There are many signs and symptoms of this progressive disease, and they tend to get worse as the child ages. The facial appearance is usually wrinkled, with a larger head in relation to their body, with a narrow face and a beak nose. The child experiences full-body alopecia. Scleroderma, a hardening and tightening of the skin on trunk and extremities of the body, is also prevalent. Since they experience hair loss, prominent scalp veins are noticeable, as well as prominent eyes. Musculoskeletal degeneration causes loss of body fat and muscle, stiff joints, hip dislocations, and other symptoms generally absent in the non-elderly population. Exams and Tests

The signs include:

- Insulin-resistance
- Skin changes similar to that seen in scleroderma (the connective tissue becomes tough and hardened)

Cardiac stress testing may reveal signs of early atherosclerosis of blood vessels.

Genetic testing can detect mutations in lamin A that cause progeria ⁽¹⁰⁾

Cause

Hutchinson-Gilford Progeria Syndrome (HGPS) is a childhood disorder caused by a point mutation in position 1824 of the LMNA gene, replacing cytosine with thymine, creating a form of the Lamin A protein which cannot be processed properly and accumulates in the cell nucleus. Lamin A is a major structural protein of the human cell nucleus.

Before the late 20th century, research on progeria yielded very little information about the syndrome. In 2003, the cause of progeria was discovered. The LMNA gene is responsible for producing lamin proteins, which provide strength and stability in cells. Lamin A and Lamin C support the nuclear envelope. When Lamin A is altered, it affects the shape and the function of the nuclear envelope. These changes cause other cells to die prematurely. Unlike "accelerated aging diseases" (such as Werner's syndrome, Cockayne's syndrome, or xeroderma pigmentosum), progeria is not caused by defective DNA repair. Because these diseases display what are considered different aspects of aging, but never every aspect, they are often called "segmental progerias".^[11] 90% of children with Progeria have a mutation on the gene that encodes Lamin A, a protein that holds the nucleus of the cell together. It is believed that the defective Lamin A protein makes the nucleus unstable. This instability seems to lead to the process of premature aging among Progeria patients. Progeria appears to occur without cause - it is not seen in siblings of affected children. In extremely rare cases more than one child in the same family may have the condition. Progeria is a rare condition that is remarkable because its symptoms strongly resemble normal human aging, but occur in young children.⁽³¹⁾⁽³²⁾

Ninety percent of children with progeria have a mutation on the gene that encodes the protein lamin A. Progeria usually occurs without cause. It is only very rarely seen in

more than one child in a family. HGPS is caused by a mutation in the gene called LMNA (pronounced, lamin – a). The LMNA gene produces the Lamin A protein, which is the structural scaffolding that holds the nucleus of a cell together. Researchers now believe that the defective Lamin A protein makes the nucleus unstable. That cellular instability appears to lead to the process of premature aging in Progeria. PRF was the driving force behind finding the gene responsible for Progeria. A group of leading scientists from The Progeria Research Foundation's Genetics Consortium was able to isolate the Progeria gene in October 2002, and in April 2003, PRF led the announcement that Progeria is caused by a mutation of the gene LMNA, or Lamin A. This gene discovery was reported in the leading scientific journal Nature.⁽³⁰⁾ The Progeria gene finding involved intensive collaboration between scientists including Dr. Leslie Gordon, PRF's Medical Director, Dr. W. Ted Brown, a world expert on Progeria and Chairman of New York's Institute of Basic Research in Developmental Disabilities' Department of Human Genetics, Dr. Tom Glover, a PRF grantee and Professor at University of Michigan's Department of Human Genetics, Dr. Francis Collins, Director of the National Human Genome Research Institute (responsible for mapping the human genome) and the senior author on the report, and first author Dr. Maria Eriksson, a postdoctoral fellow with Dr. Collins. "Isolating the Progeria gene is a major achievement for the medical research community," said Dr. Collins, "The discovery not only gives hope to children and families affected by Progeria, but also may shed light on the phenomenon of aging and cardiovascular disease."⁽²⁹⁾

Diagnosis

Diagnosis is suspected according to signs and symptoms, such as skin changes, abnormal growth, and loss of hair.⁽²⁸⁾ It can be confirmed through a genetic test. The health care professional will possibly suspect Progeria if the signs and symptoms are there - aging skin, loss of hair, stiffness of joints, etc. This can then be confirmed through a genetic test. The Progeria Research Foundation has created a Diagnostic Testing Program.⁽²⁷⁾

Treatment

No treatments have been proven effective. Most treatment focuses on reducing complications (such as cardiovascular disease) with heart bypass surgery or low-dose aspirin.^[13] Children may also benefit from a high-calorie diet. Research indicates that a chemical (hyaluronic acid) may be found in greatly elevated levels in the urine of Hutchinson-Gilford Progeria Syndrome patients.⁽²⁶⁾ The same abnormality has been found in Werner Syndrome, which is sometimes called 'progeria of the adult'. Research indicates that a chemical (hyaluronic acid) may be found in greatly elevated levels in the urine of Hutchinson-Gilford Progeria Syndrome patients. The same abnormality has been found in Werner Syndrome, which is sometimes called 'progeria of the adult'. There is no cure for Progeria but we can treat some of the symptoms. Here are some of the remedies and medicines that we give to Hayley to make her quality of life as comfortable as possible.⁽¹²⁾

Hydrotherapy. Every week we take Hayley to our local hospital for a 30 minute session in the Hydrotherapy pool. Hydrotherapy promotes relaxation, relieves pain, assists movement and enables exercise. It can also help prevent arthritis from getting worse. It is also great fun!⁽²⁴⁾

Nutrini. Hayley has a very small appetite and doesn't really enjoy eating. Each night before she goes to bed she has a 200ml bottle of Nutrini. This provides all of the nutrients essential for well-being and health.⁽¹³⁾

Pro-Cal. Pro-Cal is a new generation protein and calorie food enricher that can be added to a wide variety of food and drink to enrich the energy and protein content of the normal diet with the minimum effect on taste, volume and texture.⁽²³⁾ We add a 15g scoop to Hayleys morning cup of tea and another to her bottle of Nutrini. Each Scoop provides her with 100kcal of energy and 2g of protein as well as vital minerals such as sodium, potassium and calcium.⁽¹⁴⁾

Vitamin E. Vitamin E is a fat-soluble vitamin that protects Vitamin A and essential fatty acids from oxidation in the body cells and prevents breakdown of body tissues.⁽²²⁾ Antioxidants such as Vitamin E act to protect the cells against the effects of free radicals, which are potentially damaging by-products of the body's metabolism. Free radicals can cause cell damage that may contribute to the development of cardiovascular disease and cancer. Hayley has 4ml of Vitamin E every day.⁽²¹⁾

Aspirin. Aspirin is now accepted as an important weapon in the prevention of heart disease. Recent clinical trials have shown that aspirin reduces the risk of strokes and heart attacks. A small dose of aspirin is enough to prevent dangerous blood clotting. This is of benefit to people with narrowed coronary arteries which is common place in children with Progeria. Hayley has half of a 75mg tablet every day.⁽¹⁵⁾

Fluoride. All Progeria children have problems with thier teeth. Underdevelopment of the facial bones and the lower jaw leads to delayed eruption of the teeth, they can be small, irregularly formed or even missing and tooth decay is common. Fluoride can greatly help dental health by strengthening the tooth enamel, making it more resistant to tooth decay. Hayley has half of a 1.1mg tablet every day.⁽²⁰⁾ Growth hormone treatment has been attempted.⁽¹⁴⁾ A type of anticancer drug, the farnesyltransferase inhibitors (FTIs), has been proposed, but their use has been mostly limited to animal models.⁽¹⁵⁾ A Phase II clinical trial using the FTI Lonafarnib began in May 2007.⁽¹⁶⁾ In studies on the cells another anti-cancer drug—rapamycin caused removal of progerin from the nuclear membrane.⁽¹⁷⁾ Farnesyltransferase inhibitors (FTIs), currently used for treating cancer, might reverse the nuclear structure abnormalities that are believed to cause Progeria. Studies carried out on mice with Progeria-like signs and symptoms showed that FTIs appeared to offer some improvements. Of the 13 mice treated with FTI, only one died during the 20-week UCLS study. Dr Leslie Gordon, director of the Progeria Research Foundation, said: "This study gives us pieces of information critical to our movement toward clinical trials in children with progeria."⁽¹⁹⁾

Prognosis

There is no known cure. Few people with progeria exceed 13 years of age.⁽¹⁸⁾ At least 90% of patients die from complications of atherosclerosis, such as heart attack or stroke.⁽¹⁹⁾ Mental development is not affected. With respect to the features of aging that progeria appears to manifest, the development of symptoms is comparable to aging at a rate eight to ten times faster than normal.⁽¹⁸⁾ With respect to features of aging that progeria does not exhibit, patients show no neurodegeneration or cancer predisposition.

They also do not develop the so-called "wear and tear" conditions commonly associated with aging, such as cataracts (caused by UV exposure) and osteoarthritis (caused by mechanical wear).^[12] Although there may not be any successful treatments for progeria itself, there are treatments for the problems it causes, such as arthritic, respiratory, and cardiovascular problems⁽²⁵⁾

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