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Progeria-The rapid aging disease

Arya Lekshmi Kg, Athira Valsalan P, Treesa Pearl

Pharmacist, Poyanil Hospital, Punalur, Kollam, Kerala, India

Abstract
The effect of progeria is most commonly seen in children. It is an extremely rare genetic disorder in which symptoms resembling aspects of aging are manifested at a very early age. Progeria is one of several progeroid syndromes caused due to the mutation in the gene Lamin A. Progeria was first described in 1886 by Hutchinson. It was also described independently in 1897 by Gilford. The condition was later named Hutchinson–Gilford progeria syndrome. The word *progeria* comes from the Greek words "pro" (πρό), meaning "before" or "premature", and "gēras" (γῆρας), meaning "old age". As there is no complete cure, few people with progeria exceed 13 years of age. At least 90% of patients die from complications of atherosclerosis, such as heart attack or stroke. Mental development is not adversely affected; in fact, intelligence tends to be average to above average 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. Sufferers of progeria have normal reproductive development and there are known cases of women with progeria who had delivered healthy off springs.

Keywords: progeria, Aging, Lamin A, farnesyl transferase inhibitors, mutation

1. Introduction
Progeria is a rare genetic disorder of childhood marked by slowed physical growth and characteristic signs (such as baldness, wrinkled skin, atherosclerosis etc.) of rapid aging with death usually occurring around puberty. Progeria is due to a single-letter "misspelling" in a gene on chromosome that codes for lamin A, a protein that is a key component of the membrane surrounding the cell's nucleus. A single mistake in these gene causes it to make an abnormal protein, called progerin, they break down more easily. Progeria is not inherited, or passed down in families. Most children with classic progeria harbor exactly the same misspelling in the lamin A (LMNA) gene, a substitution of just a single DNA base -- a change from cytosine (C) to thymine (T) -- among the gene's 25,000 base pairs. In a few progeria patients there may be a different single base substitution such as guanine (G) to adenine (A) just two bases upstream. Unlike many genetic mutations, progeria isn't passed down in families. Rather, the gene change is a chance occurrence that researchers believe affects a single sperm or egg just before conception. Neither parent is a carrier, so the mutations in the child's genes are new (de novo).

1.1 Epidemiology
The proportion of children with HGPS per total population is one in eighteen million [Gordon *et al.* 2014]. The estimated birth incidence for HGPS is one in four million births with no observed differences based on ethnic background (Hennekam 2006). A study from the Netherlands has shown an incidence of 1 in 4 million births. Progeria Research Foundation data bases shows that there is an estimated 200-250 children living with progeria worldwide and 103 of them have been identified as of April 2013.
Progeria is almost never passed on from affected parent to child, as they have very short life span. There have been only two cases in which a healthy person was known to 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, though not the classical HGPS type. This family was the subject of a 2005 Bodyshock documentary titled *The 80 Year Old Children*. The Vandeweert family of Belgium has two children, Michiel and Amber, with classic HGPS. 97%of people with HGPS are Caucasian. Males are 1.5%times more likely to have HGPS than females.

1.2 Etiopathogenesis
Progeria is due to mutation of a single gene, known as lamin A (LMNA), makes a protein necessary for holding the center (nucleus) of a cell together and any defect on these gene makes the cells unstable and proceeds the process of aging.

Table 1

Steps in normal cell	Steps in cell with progeria
The gene LMNA encodes a protein called prelamin A.	
Prelamin A has a farnesyl group attached to its end.	
Farnesyl group is *removed* from prelamin A.	Farnesyl group remains *attached* to prelamin A.
Normal form is called lamin A.	Abnormal form of prelamin A is called progerin.
Lamin A is not anchored to the nuclear rim.	Progerin is anchored to the nuclear rim.
Normal state of the nucleus.	Abnormally shaped nucleus.

In normal conditions, the *LMNA* gene codes for a structural protein called prelamin A which undergoes a series of processing steps before becoming its final form, called lamin A. In one of these steps, after prelamin A is made in the cytoplasm, an enzyme called farnesyl transferase attaches a farnesyl functional group to its carboxyl-terminus. The farnesylated prelamin A is then transported through a nuclear pore to the interior of the nucleus. The farnesyl group allows prelamin A to attach temporarily to the nuclear rim. [*citation needed*] Once the protein is attached, it is cleaved by a protease, thereby removing the farnesyl group along with a few adjacent amino acids. Failure to remove this farnesyl group permanently affixes the protein to the nuclear rim. After cleavage by the protease, prelamin A is referred to as lamin A. Lamin A, along with lamin B and lamin C, makes up the nuclear lamina, which provides structural support to the nucleus.

In 2003, the cause of progeria was discovered to be a point mutation in position 1824 of the *LMNA* gene, in which cytosine is replaced with thymine.[16] This mutation creates a 5' cryptic splice site within exon 11, resulting in an abnormally short mature mRNA transcript. This mRNA strand, when translated, yields an abnormal variant of the prelamin a protein whose farnesyl group cannot be removed and the abnormal protein, referred to as progerin, is permanently affixed to the nuclear rim, and therefore does not become part of the nuclear lamina. Without lamin A, the nuclear lamina is unable to provide the nuclear envelope with adequate structural support, causing it to take on an abnormal shape.

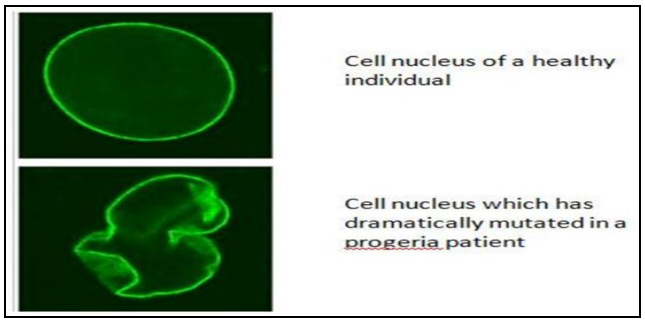

Fig 1

1.3 Clinical manifestations and complications

Children with progeria are born looking healthy and the symptoms will appear around 18-24 months. Limited growth, full-body alopecia and a small face with a shallow recessed jaw, and a pinched nose. Wrinkled skin, atherosclerosis, kidney failure, loss of eyesight, and cardiovascular problems.

Scleroderma, a hardening and tightening of the skin on trunk and extremities of the body. Small, fragile bodies, like those of elderly people. The face is usually wrinkled, with a larger head in relation to the body, a narrow face and a beak nose. Prominent scalp veins are noticeable (made more obvious by alopecia), as well as prominent eyes. Musculoskeletal degeneration causes loss of body fat and muscle, stiff joints, hip dislocations. As children with progeria get older will suffer with bone loss, hardening of the arteries, and heart disease. Children with progeria usually die of heart attacks or strokes.

Most children with progeria die of complications related to atherosclerosis, including:

- Problems with blood vessels that supply the heart (cardiovascular problems), resulting in heart attack and congestive heart failure
- Problems with blood vessels that supply the brain (cerebrovascular problems), resulting in stroke

1.4 Diagnosis

It include physical examination (such as skin changes, abnormal growth, and loss of hair). Test for hearing and vision. Measurement of pulse and blood pressure, and compare the child's height and weight to other kids the same age.

Blood test and a genetic test for LMNA mutations can confirm the diagnosis of progeria. A sample of the patient's blood is taken and analyzed in a laboratory for a mutation in the lamin A (LMNA) gene.

Before genetic testing was available, doctors diagnosed the condition solely on the patient's physical symptoms. Therefore, genetic testing allows doctors to diagnose HGPS at an earlier age, before all of the characteristic symptoms are seen.

1.5 Treatment

No treatment has yet proven effective. Most treatment options have focused on reducing complications (such as cardiovascular disease) with coronary artery bypass surgery and low-dose aspirin.

Growth hormone treatment has been attempted due to its potent anabolic properties and growth promoting effects.

Morpholinos has also been used to reduce progerin production.

A type of anticancer drug, the farnesyltransferase inhibitors (FTIs), has been proposed, but their use has been mostly limited to animal models.

Farnesyltransferase inhibitors (FTIs) are drugs that inhibit the activity of an enzyme needed in order to make a link between progerin proteins and farnesyl groups. This link generates the permanent attachment of the progerin to the nuclear rim. In progeria, cellular damage can be appreciated because that attachment takes place and the nucleus is not in a normal state. Lonafarnib is an FTI, it can avoid this link, so progerin cannot remain attached to the nucleus rim and it now has a more normal state but the delivery of Lonafarnib is not approved by the US Food and Drug Administration and it can only be used in certain clinical trials.

Sirolimus, is a macrolide. Studies concerning Sirolimus conclude that it can minimize the phenotypic effects of progeria fibroblasts. Other observed consequences of its use are: abolishment of nuclear blebbing, degradation of progerin in affected cells and reduction of insoluble progerin aggregates formation.

Medication, Physical and occupational therapy, dietary changes along with low dose aspirin helps to prevent the risk of heart attacks and stroke.

Coronary bypass surgery or angioplasty were done to slow the progression of heart disease in some cases.

At home. Kids with progeria are more likely to get dehydrated, so they need to drink plenty of water, especially when they're sick or it's hot. Small meals more often can help them eat enough, too. Cushioned shoes or inserts can ease discomfort and encourage your child to play and stay active.

2. Conclusion

Progeria is one of the disease that causes premature aging and death of the affected person. Most of the victims are children and the expectancy of their life span is very short. As the rei no effective treatment for=r the disease, medications are taken to reduce the symptoms only. To treat and cure the disease I an efficient way it is need to study the etiology, cellular and molecular mechanisms that accelerate the ageing process leading to rapid progression of the disease. Early diagnosis of the progeria will preventing the worsening and complications of the disease.

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