DOI: 10.56511/JIPBS.2015.v2.i03.pp261-265

Journal of Innovations in Pharmaceuticals and Biological Sciences
www.jipbs.com

JIPBS

ISSN: 2349-2759

Review Article

A Review on Progeria

Deepu S D*[1], Ajin Sam[1], Vishnu R Nair[1], Tony Kuriakose[1], Jiju V[1], Santhosh M Mathews[1]

[1]Nazareth College of pharmacy, Othera, Thiruvalla.

Abstract

Progeria (Hutchinson–Gilford progeria syndrome, HGPS, progeria syndrome) is an extremely rare genetic disorder wherein symptoms resembling aspects of aging are manifested at a very early age. Classical Hutchinson–Gilford progeria syndrome 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. 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. Progeria may be a de novo dominant trait. It develops during cell division in a newly conceived zygote or in the gametes of one of the parents. It is caused by mutations in the LMNA (lamin A protein) gene on chromosome 1; the mutated form of lamin A is commonly known as progerin.

Key words: Progeria, Prelamin A, lamin A, HGPS, Morpholinos

***Corresponding Author: Deepu S D,** Nazareth College of pharmacy, Othera, Thiruvalla.

1. Introduction

Progeria is an extremely rare genetic disorder wherein symptoms resembling aspects of aging are ma*nifested at a very early age which* is one of several progeroid syndromes. The word progeria comes from the Greek words "pro", meaning "before" or "premature", and "gēras", meaning "old age". Those born with progeria typically live to their mid teens to early twenties. It is a genetic condition that occurs as a new mutation, and is rarely inherited, as carriers usually do not live to reproduce. Although the term progeria applies strictly speaking to all diseases characterized by premature aging symptoms, and is often used as such, it is often applied specifically in reference to Hutchinson–Gilford progeria syndrome (HGPS)[2].

Incidence

The disorder has a very low incidence rate, occurring in 1 per 8 million live births. Scientists are particularly

©JIPBS, All rights reserved

interested in progeria because it might reveal clues about the normal process of aging. Progeria was first described in 1886 by Jonathan Hutchinson.It was also described independently in 1897 by Hastings Gilford. The condition was later named Hutchinson–Gilford progeria syndrome.

Causes

In normal conditions, the LMNA gene codes for a structural protein called prelamin A. There is a farnesyl functional group attached to the carboxyl-terminus of its structure. The farnesyl group allows prelamin A to attach temporarily to the nuclear rim. Once the protein is attached, the farnesyl group is removed. Failure to remove this farnesyl group permanently affixes the protein to the nuclear rim. Without its farnesyl group, 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. The cause of progeria was discovered to be a point mutation in the position 1824 of the LMNA gene, in which cytosine is replaced with thymine. 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. Because its farnesyl group cannot be removed, this 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. Since the support that the nuclear lamina normally provides is necessary for the organizing of chromatin during mitosis, weakening of the nuclear lamina limits the ability of the cell to divide. Unlike "accelerated aging diseases", progeria is not caused by defective DNA repair. Because these diseases cause changes in different aspects of aging, but never in every aspect, they are often called "segmental progerias." [2]

Steps in normal cell	**Steps in cell with progeria**
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

Signs and Symptoms

Children with progeria usually develop the symptoms during their first few months of Life.



Figure 1. A young girl with progeria (left). A progeric cell nucleus (right, bottom) and a healthy cell nucleus (right, top).

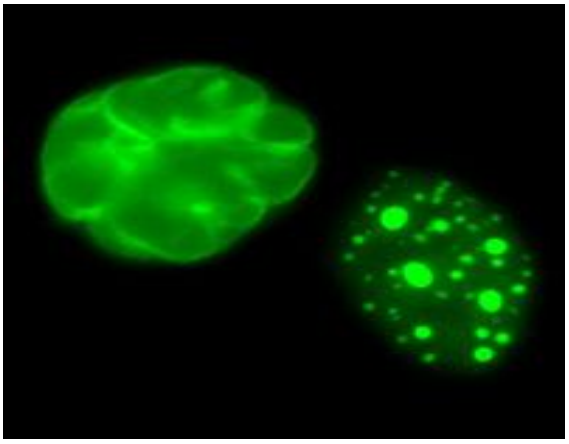


Figure 2. Untreated cells from children with the genetic disease progeria (left) compared to similar cells treated with FTIs.

- The earliest symptoms may include a failure to thrive and a localized scleroderma-like skin condition.
- As a child ages past infancy, additional conditions become apparent usually around 18–24 months.
- Limited growth, full-body alopecia (hair loss), and a distinctive appearance (a small face with a shallow recessed jaw, and a pinched nose) are all characteristics of progeria.
- Signs and symptoms of this progressive disease tend to become more marked as the child ages.
- Later, the condition causes 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, is prevalent.
- People diagnosed with this disorder usually have 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, and other symptoms generally absent in the non-elderly population. Individuals usually retain normal mental and motor development.

Diagnosis

Diagnosis is suspected according to signs and symptoms, such as skin changes, abnormal growth, and loss of hair. A genetic test for LMNA mutations can confirm the diagnosis of progeria. Since the symptoms are very noticeable, it's likely that pediatrician will spot them during a routine checkup.

If changes in *a* child that seem like symptoms of progeri*a, make an appointment with pediatrician. He will* do a physical exam, test hearing and vision, measure pulse and blood pressure, and compare child's height and weight to other kids *of* the same age.

Afterward, if *the* pediatrician is concerned, *the parent* may need to see a specialist in medical genetics, who can confirm the diagnosis with a blood test [5].

Treatment

- ✓ No treatment has proven effective.
- ✓ Most treatment focuses on reducing complications (such as cardiovascular disease) with coronary artery bypass surgery or low-dose aspirin.
- ✓ Growth hormone treatment has been attempted.
- ✓ The use of Morpholinos has also been attempted in order to reduce progerin production. Antisense Morpholino oligonucleotides specifically directed against the mutated exon 11–exon 12 junction in the mutated pre-mRNAs were used.
- ✓ **Low-dose aspirin**: A daily dose of aspirin may be recommended to help prevent heart attacks and stroke. Children should only take aspirin under

the strict supervision of a healthcare professional because serious side effects may occur.

- ✓ **Physical therapy**: Physical therapy may be beneficial for children with HGPS because they typically have low muscle tone and experience joint stiffness and hip problems. A variety of techniques, including exercises, stretches, traction, electrical stimulation, and massage, are used during physical therapy sessions. A therapist may also teach parents or caregivers how to exercise a baby's muscles.
- ✓ **High-calorie dietary supplements**: High-calorie dietary supplements may be recommended to help prevent weight loss and ensure adequate nutrition. Supplements should be taken under the supervision of a healthcare professional. A pediatrician may also recommend a nutritionist to help ensure that the child is receiving the proper vitamins and minerals.
- ✓ **Feeding tube**: Some infants with HGPS may have difficulty feeding due to physical abnormalities. In such cases, a feeding tube may be needed to ensure that the child receives proper nutrition.
- ✓ **Removal of baby teeth**: A child's permanent teeth might start coming in before the baby teeth have fallen out. If this happens, a dentist usually removes the baby teeth in order to prevent complications, such as overcrowding [5].

New Drugs

New drugs, called farnesyltransferase inhibitors (FTIs), which were originally developed to treat cancer, may help treat HGPS in the future. Early studies have produced promising results. In laboratory and animal studies, these drugs have effectively corrected cell defects that cause HGPS. Specifically, they have been shown to improve nuclear shape by preventing the abnormal protein from reaching the scaffolding of the cell nucleus. However, additional human studies are needed to determine if FTIs are safe and effective for people with HGPS. Currently the use of FTIs use has been mostly limited to animal models. A Phase II clinical trial using the FTI lonafarnib began in May 2007.

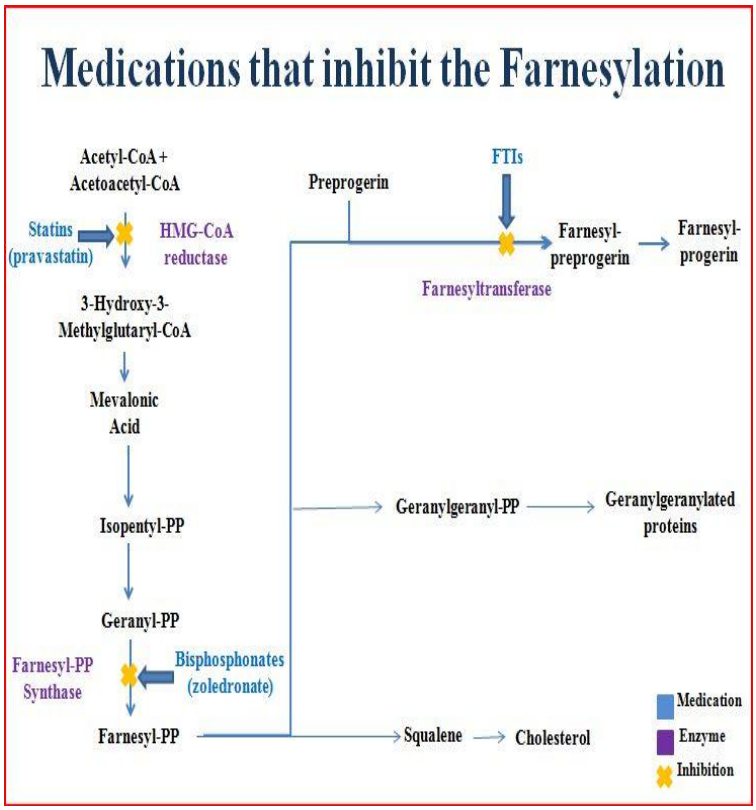
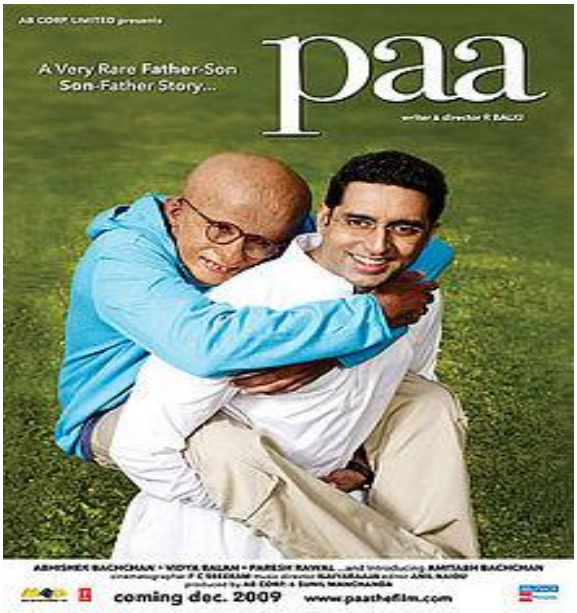


Figure 3. Medication that inhibit the farnesylation

Conclusion

As there is no known 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 normal to above average. 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. With respect to

features of aging that progeria does not exhibit, patients show no neuro degeneration 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). Although there may not be any successful treatments for progeria itself, there is 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 offspring. A Bollywood movie, Paa was released in 2009 based on a rare genetic condition known as progeria and places emphasis on a father-son relationship; in it, the lead (Amitabh Bachan) played a 13-year-old child affected by progeria.



References

1. The Free Dictionary: Progeria
2. Progeria, Incidence of Progeria and HGPS
3. James, William; Berger, Timothy; Elston, Dirk (2005). Andrews' Diseases of the Skin: Clinical Dermatology (10th Ed.). Saunders. p. 574. ISBN 0-7216-2921-0
4. Rapini, Ronald P.; Bolognia, Jean L.; Jorizzo, Joseph L. (2007). Dermatology: 2-Volume Set. St. Louis: Mosby. ISBN 1-4160-2999-0
5. http://articles.latimes.com/1985-05-30/news/mn-4953_1_rare-aging-disease
6. http://articles.orlandosentinel.com/1985-05-28/news/0300240121_1_progeria-casey-survivor
7. http://www.nytimes.com/2005/01/30/magazine/30PROGERIA.html?pagewanted=4&_r=0