AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

A Comprehensive Review on Progeria

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ABSTRACT

Our life span is genetically programmed and it is possible that a defect in produced proteins encoded by the 'longevity' gene is a cause of aging. Progeria which is a rare, fatal genetic condition which affects between one in four million and one in eight million children of both sexes equally and characterized by premature and accelerated aging. The appearance and physiology of these children resembles to elderly people but they typically have life span to their mid teens. It is also known as the Hutchinson-Gilford syndrome, which was initially reported by Johnathan Hutchinson in 1886 and further described by Hastings Gilford in 1904. It is an autosomal recessive disorder, which means an individual has inherited a mutated gene from both parents. It is added to the expanding catalogue of 'laminopathies', diseases caused by mutations affecting nuclear lamina proteins known as lamin A (LMNA). Currently, there are about 50 known cases of Progeria in the world and most Progeria patients die at around 13 years of age. Treatment usually includes aspirin which helps prevent the atherothrombotic events, stroke and heart attacks by hindering platelet aggregation. Vitamin supplementation, Fluoride supplements are recommended. A Study of Zoledronic acid, Pravastatin, and Lonafarnib for Patients with Progeria is ongoing, it is under phase II.

Keywords: Progeria, Hutchinson Gilford Progeria Syndrome, Premature Aging, Aspirin, Atherothrombotic, lamin A.

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Received 17 January 2016, Accepted 27 January 2016

Please cite this article as: Srikrishna T *et al*., A Comprehensive Review on Progeria. American Journal of PharmTech Research 2016.

INTRODUCTION

Progeria is also known as Hutchinson-Gilford Progeria Syndrome, Werner Syndrome (adultform), Cockayne Syndrome, and Rothmund-Thomson Syndrome. Progeria is an extrely rare genetic disorder wherein symptoms resembling aspects of aging are manifested at a very early age which is one of several progeroid syndromes. progeria is also a rare hereditary disease that affects the skin, musculoskeletal system and vasculature. The word progeria names stems from thelatin and Greek words "pro", meaning "before" or "premature", and "gēras", meaning "old age". Progeria occurs in two forms; Hutchinson -Gilford syndrome and Werner Syndrome. progeria the aging process to approxiamately 7 times the normal rate. 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[1].

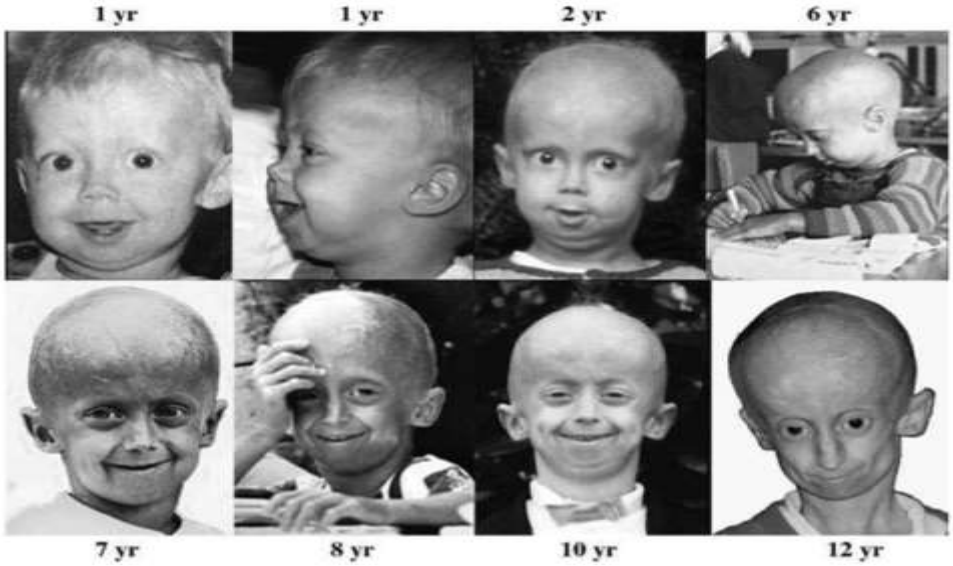

Fig: Dutch Patient at the age of 1 year, 1 year, 2 years, 6 years, 7 years, 8 years, 10 years, and 12 years.

Figure 1: Dutch Patient at the age of 1 year, 2 years, 6 years, 7 years, 8 years, 10 years and 12 years

Children with progeria look normal during their first years of life, but soon symptoms begin to appear. By the age of 1 or 2, their hair turns lighter in colour, and eventually begins to fall out. By 3 or 4, they are almost completely bald, thin skinned, wrinkled and spotted in various parts of their body, with a stooped appearance and large veiny heads, a pinched nose, delayed tooth formation, stiffness of joints, hip dislocations, cardiovascular problems, arteriosclerosis, wrinkled/aged-looking skin, dwarfism. The children develop early arteriosclerosis, high blood pressure heart disease, and stroke. They do not, however, typically show other characteristics of aging such as

Alzheimer's disease, and arthritis of the hips unless caused by prior hip dislocations. They very rarely reach a height of 107cm or a weight of 18 kg. People with progeria seldom make it to the approximate age of 30, and for most the lifespan is the early teens. They all bear are markable resemblance to each other. They both look alike and are affected by very similar symptoms. Although their physical appearance is beyond their years their mental development and intelligence is at the normal place for their actual age[2].

History

Dr. Jonathan Hutchinson recorded the first Progeria case in 1886 and in 1904; Dr. Hastings Gilford recorded another case. Progeria is a rare genetic condition that affects one in eight million new-borns worldwide. It can occur without any cause and can be seen in a family with no history of progeria. In very rare cases, more than one child from the same family can be affected by the disease.

In the nearly 120 years since it was first identified, more than 130 cases have been reported in the scientific literature., 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 new-borns. 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.It is estimated that 97% of all children with Progeria are Caucasian and males out number females by a 1.5:1 ratio. Sadly, death can occur between the ages of 7-28, but the average age is13.4 years. It is estimated that 80% of Progeria deaths are caused by congestive heart failure or heart attacks. While the average life expectancy of a child with Progeria is less than 14 years, it is believed that the oldest case ever recorded 26 years of age. Not true. The oldest case ever recorded was a Japanese man who lived with the disease for 45years. In this particular case, the child did not show signs of growth retardation until around 12years of age. It was noted, however, that his head was larger than normal at the age of one and he did experience hair loss in childhood, but enjoyed a rather normal life for 12 years. By age 20, this particular subject had total Alopecia and aging began to accelerate. The subject died at the age of 45 from myocardial infarction[3].

Progeroid Syndromes

Progeria**,** any of several rare human disorders associated with premature aging. The two major types of progeria are Hutchinson-Gilford syndrome, which has its onset in early childhood,

and Werner syndrome (or adult progeria), which occurs later in life. Other progeria syndromes are Dyskeratosis congenital, Trichothiodystrophy or Tay's syndrome and Cockayne's syndrome.

1) Hutchinson-Gilford Progeria

- Nearly 1 out of 8 million children suffer from this syndrome.
- The child with this syndrome appears normal at birth, but the symptom begins to appear at the age of 6 to 12 months.
- The baby fails to gain weight and also there are changes in skin[4].

Characteristics of Hutchinson-Gilford syndrome

- Face and Head – Prominent eyes and scalp veins, baldness, delayed tooth formation, small jaw.
- Bones – short stature, hip dislocations, joint stiffness, thin limbs and prominent joints.
- Artery and heart disease.
- About 97% affected children are Caucasian.
- All children who have this syndrome share a similar appearance, whether they are of same race or ethnic background.
- Children with this syndrome generally survive to an age of 13 years and most of them succumbing to heart diseases[5].

2) **Werner Syndrome**

- This syndrome is the most common type of progeria.
- It occurs in about 1 person out of 1 million people.
- When a child in adolescence fails to have a normal growth is the identification ofWerner syndrome.
- Hence, the result is the young person looks elderly.

Characteristics of Werner Syndrome

- There is a remarkable difference in a person's real age and appearance Werner Syndrome
- Face and head – Face wrinkling, balding and greying of hair, cataracts, small jaw and sunken cheek, and voice of high pitch.
- Bones – small stature, osteoporosis, weakness.
- Cancer and diabetes are common in this syndrome.
- Werner syndrome mostly occurs in Sardinian and Japanese people.
- People with the syndrome mostly survive to an age of 46, mostly succumbing to cancer and heart diseases[6].

3)**Dyskeratosis congenital**

DKC is an inheritable bone-marrow failure disorder linked to mutations in DKC1, TERC, TERT, NOP10, NHP2, TIN2 or TCAB1 genes16, implicating the physiology of telomeres.

4) **Trichothiodystrophy or Tay's syndrome**

Trichothiodystrophy (or Tay's syndrome) is an autosomal recessive disease identified by small stature, mental and overall growth retardation, ocular defects, brittle hair and other developmental abnormalities like congenital ichthyosisformerythroderma. Patients have abnormal production of transcription factor II H (TFIIH), a general transcription factor active in basal transcription and nucleotide excision repair, due to mutations in genes encoding any of the 3 subunits of TFIIH—ERCC2 (XPD), ERCC3 (XPB), and GTF2H5 (TTDA).

5) Cockayne syndrome

Cockayne syndrome, another rare congenital disorder, is characterized by growth failure, atypical photosensitivity and importantly impaired development of the nervous system. Mutations in any of the ERCC6 and ERCC8 genes bring about defect in DNA repair mechanism which eventually precipitates this disease.By the age of two years, growth and development of the individual becomes abnormal. The distinctive physical appearance of cachectic dwarfism with sunken eyes, reduction of the skin and hair thickness and an arched standing posture characterizes the ageing process. Neuropathological investigations demonstrate widespread demyelination in the central and peripheral nervous systems of the patients. There is also neuronal loss in the cerebral cortex and cerebellum, and calcification around capillaries in the cerebral cortex and basal ganglia. These children show cognitive impairment and intellectual deficits which often worsen with age 20[7].

Epidemiology

HGPS is a very rare disorder prevalent in 1 in four million births. Currently there are 35-45known cases in the whole world. Since 1886 approximately 100 cases have been identified around the world. White persons represent 97% of reported patients. The reason for this racial disparity is unknown. HGPS has a slight male predilection; the male-to-female ratio is 1.5:1. Generally the disease does not pass from parents to child as the victim dies before the age of reproduction.It is usually caused by a new (sporadic) mutation during the early division of the cells in the child. It is usually genetically dominant; therefore, parents who are healthy will normally not pass it on to their children. Till now two cases have been noted in which healthy parents carried mutated LMNA gene that caused Progeria in their child. Very rarely the disease is present in more than one member of family but an Indian family has five children suffering from the disease. In a Belgian family there are two children having the disorder[8].

Causes of Progeria

Gene Mutation

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[9].

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"[10].

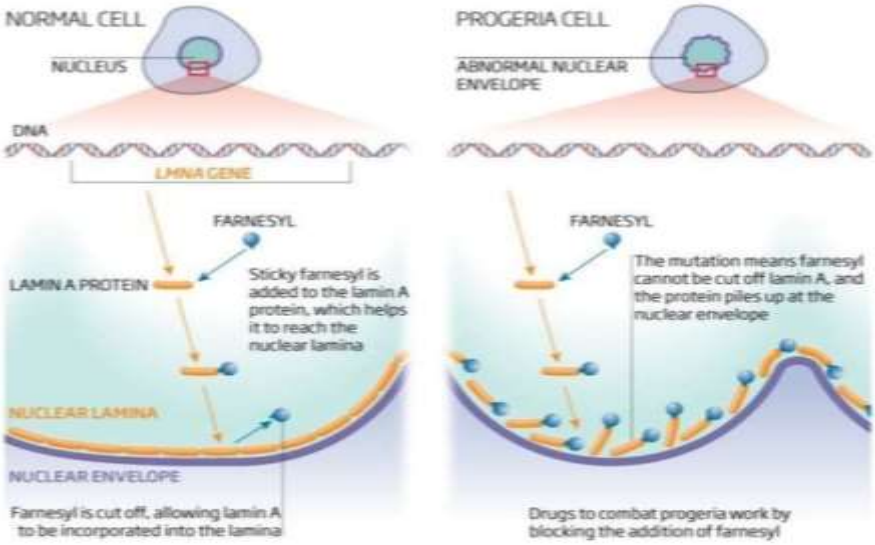

Figure 2 : Normal cells Vs Progeria cell

Is Progeria Hereditary?

Experts do not believe that Progeria is hereditary. They say it is due to a rare gene change which happens purely by chance. A non-twin sibling runs the same risk of having Progeria as any other child from another family. In about 1 in every 100 cases of HGPS the syndrome is passed down to the next generation within the same family[11].

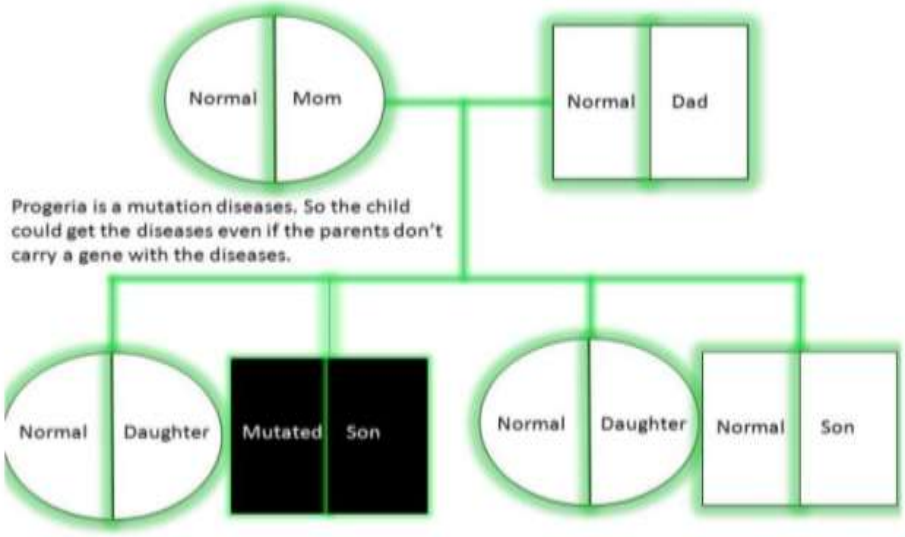

Figure 3 : Progeria mode of inheritance

Signs and Symptoms

Children with Progeria usually develop the symptoms during their first few months of Life. The following are the overall symptoms of Progeria:

- 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[12].
- 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.

Summary of gene mutations leading to various progeroid syndromes with their clinical symptoms[13]

Syndrome	Mutation in gene	Clinical symptoms
Hutchinson-Gilford Progeria syndrome	LMNA3-5	Growth retardation mostly evident within a year of birth, skin atrophy, alopecia, osteolysis, cardiovascular complications, etc.
Werner's syndrome	WRN12	Symptoms appear mostly during early teenage years; development of cataract, atherosclerosis, skin atrophy, osteoporosis, etc.
Trichothiodystrophy or Tay's syndrome	ERCC2, ERCC3 or GTF2H518	Growth and mental retardation, congenital ichthyosiformerythroderma, brittle hair.
Cockayne's syndrome	ERCC6; ERCC819	Growth failure, atypical photosensitivity, impaired development of the nervous system, poor cognitive skills, loss of hearing and visual abilities, etc.
Dyskeratosiscongenita	DKC1, TERC, TERT, NOP10, NHP2, TIN2	Nail dystrophy, abnormal skin pigmentation, mucosal leukoplakia and pulmonary

	or TCAB116	complications.

Outlook (Prognosis)

Progeria is associated with a short lifespan. The average patient survives to the early teens. However, some patients can live up to 30 years. The cause of death is usually related to the heart or a stroke as a result of the progressive atherosclerosis. Mental development is not affected. The development of symptoms is comparable to aging at a rate six to eight times faster than normal, although certain age-related conditions do not occur. Specifically, patients show no neurodegeneration or cancer predisposition. They do not develop "wear and tear" conditions commonly associated with aging, like cataracts and osteoarthritis years[14].

Complications

Children with progeria usually develop severe hardening of the arteries. This is a condition in which the walls of their arteries — blood vessels that carry nutrients and oxygen from the heart to the rest of the body — stiffen and thicken, often restricting blood flow.

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.

Other health problems frequently associated with aging — such as arthritis, nearsightedness and increased cancer risk — do not develop as part of the course of progeria[15].

Diagnosis

Many other premature aging syndromes, which are called progeroid syndromes and which also mimic senescence, need to be distinguished from progeria. Neonatal progeroid syndromes are evident at birth and include wiedemann-rautenstrauch syndrome, hallermanstreiff syndrome and debarsy syndrome. Others, including mandibuloacral dysplasia or cockayne syndrome are diagnosed later in life, although they may have a neonatal onset.

Clinical Diagnosis

The diagnosis of a Hutchinson-Gilford progeria syndrome (HGPS) should be considered in individuals who have the following features[16, 17]:

- **Growth**
  - Short stature (<3rd percentile), lifelong.
  - Weight (<3rd percentile), lifelong.

- Weight distinctly low for height.
- Head disproportionately large for face.
- Thin, high-pitched voice.

- **Body fat**
- Diminished subcutaneous fat globally, with the following sequellae:
  - Prominent scalp veins.
  - Prominent veins over most of body.
  - Circumoral cyanosis.
  - Prominent eyes.
  - Lack of ear lobes in some not all cases.
- **Skin/hair/nails/eyes**
  - Taut, dry skin that is variably pigmented (spotty)
  - Sclerodermatous" skin over lower abdomen and proximal thighs
  - Irregular small out pouchings of skin over lower abdomen and/or proximal thighs
  - Generalized alopecia with sparse downy hairs on the occiput
  - Loss of eyebrows and sometimes eyelashes
  - Dystrophic fingernails and toenails
  - Nocturnal lagophthalmos (the inability to fully close the eye) and, in a minority of cases, corneal ulceration due to exposure keratitis
  - Thin lips
- **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 atherosclerosis with widely
- variable age of clinical manifestation resulting in myocardial infarction and stroke

- **Other**
  - Prominent eyes
  - Lagophthalmos
  - Wide-based, shuffling gait
  - Failure to complete secondary sexual development

Laboratory Studies

Urinary hyaluronic acid testing

Chemical tests may reveal elevated levels of chemical hyaluronic acid in the urine as well as certain fatty compounds, and reduced levels of certain primary antioxidant enzymes in the blood. This may also increase likelihood of death, as one cause of aging is believed to be a buildup of oxidants in the blood over time. Although urinary hyaluronic acid has been reported to be increased in most children with HGPS theme asurement is now regarded as unreliable and is not recommended for diagnosis.

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 new Diagnostic Program whose first goal is to establish a Progeria cell and tissue bank to assist in further research. Scientists are exploring possibilities of using existing drugs to block or reduce production of the abnormal Lamin A protein in children with Progeria. Today the only treatment for Progeria patients is administering a low dose of aspirin throughout their lives. Aspirin may help prevent atherothrombotic events, stroke and heart attacks by hindering platelet aggregation. Currently there is no cure for the disease[18].

Imaging Studies

Diagnosis currently depends upon recognition of clinical and radiographic findings. However, a truncating mutation within the lamin A gene has recently been reported in the majority of the patient with Hutchinson- Gilford progeria; this genetic anomaly may lead to molecular diagnosis of the disease. The characteristic radiological abnormalities are to be found in the skull, thoracic cage, long bones and phalanxes. The cranial bones tend to be hypoplastic and the fontanels and sutures remain open longer than expected. Wormain bones are common. Thinning and resorption of the distal clavicles is the most consistent abnormality to be found in the thorax. Narrowing of

the posterior ribs is frequent. The long bones are slender with these cortices. Severe coxavara is a consistent finding, and moderate genu valgum is frequently present. The progressive bone loss from the distal phalanxes of the fingers and toes is one of the hallmarks of the disease[19].

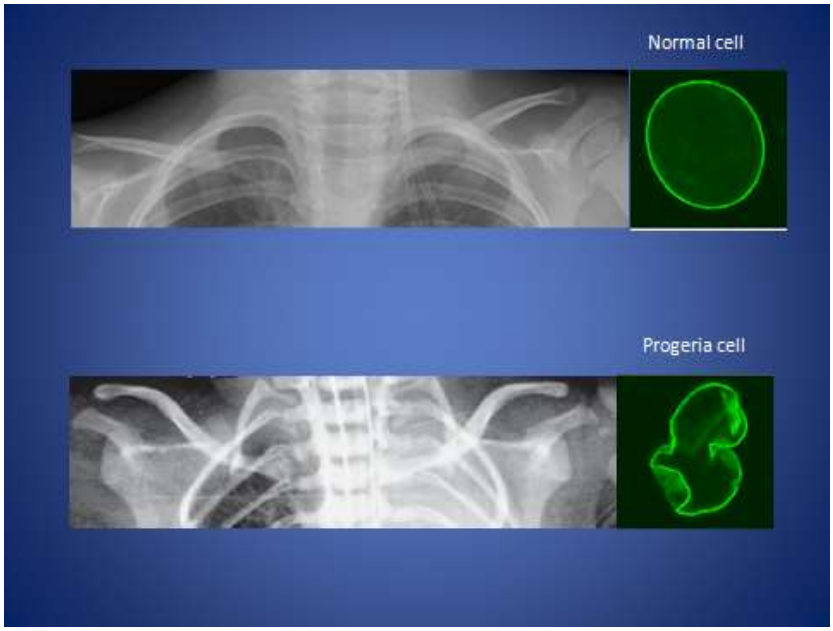

Figure 4: Imaging Studies

Other Methods

Prenatal Testing

Prenatal diagnosis for HGPS is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing.

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 germ line mosaicism 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)

Pre implementation genetic diagnosis may be available for families in which the disease-causing mutation has been identified in an affected family member for laboratories offering PGD.

Other Tests

Serial ECG and echocardiography should be performed to monitor for coronary artery disease and congestive heart failure.

Treatment[20, 21]

There is presently no treatment for Progeria. Support groups are available for the families of children with progeria. Treatment is symptomatic and aimed at providing psychological support. Palliative measures such as wearing a wig may be beneficial.

- 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.
- **Surgery:** Some children may have coronary bypass surgery or angioplasty to slow the progression of heart disease.

First Successful Treatment for Progeria

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[22].

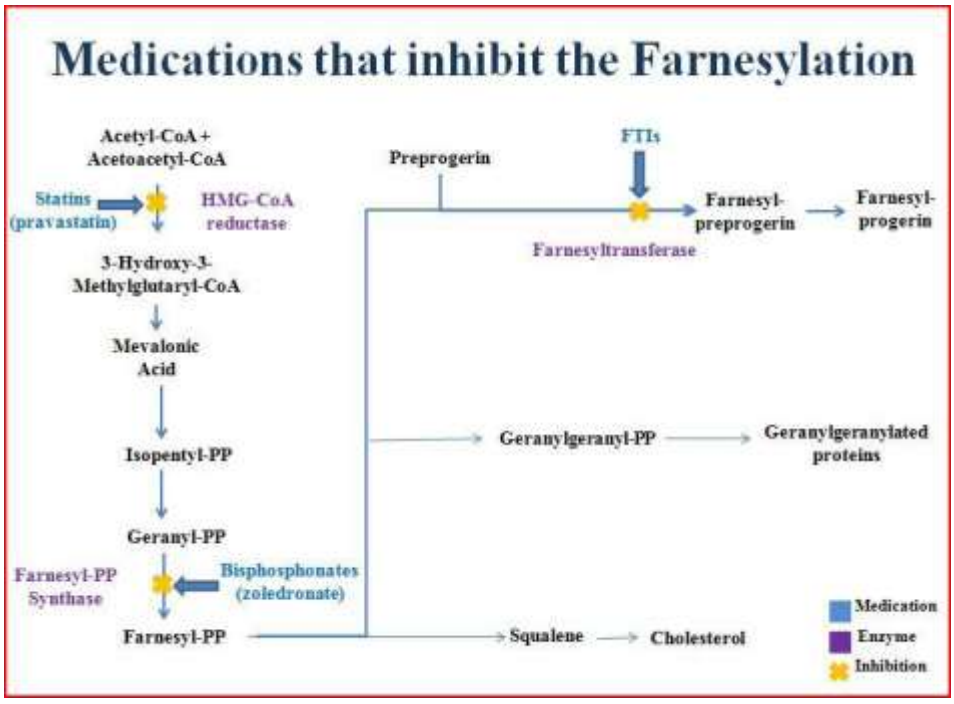

Figure 5: Medications that inhibit the Farnesylation

INCIDENCE

INTERNATIONAL

HGPS is a rare disease with a reported prevalence of 1 in 8 million births. The true prevalence, however, has been suggested to be closer to 1 in 4 million births because many cases likely go undiagnosed or are misdiagnosed. The incidence in the Netherlands over the last century was 1:4,000,000. Approximately 100 cases of HGPS have been reported in the literature.

Mortality/Morbidity

Morbidity and mortality in persons with HGPS occur primarily as a result of atherosclerosis of the coronary and cerebrovascular arteries, with at least 90% of patient deaths directly related to complications of progressive atherosclerosis. The average life expectancy for a patient with HGPS is 13 years, with an age range of 7-27years.

- Cardiovascular complications include myocardial infarction and congestive heart failure. Interstitial fibrosis, diffuse myocardial fibrosis, and calcification of the mitral and aortic valves may occur.
- Cerebrovascular complications occurring as a result of cerebrovascular infarction include hemiplegia, subdural hematoma, and seizures.
- Other causes of morbidity and mortality include marasmus, loss of mobility, and inanition.

Sex Ratio

HGPS has a slight male predilection; the male to-female ratio is 1.5:1.

Age

Clinical manifestations of HGPS may not be recognized or apparent at birth, although many affected children present with sclerodermatous skin changes. Delayed recognition of the characteristic facial features along with the cutaneous and musculoskeletal manifestations may not occur until age 6-12 months or older, when the development of failure to thrive engenders a more thorough evaluation.

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. Sufferers of progeria have normal reproductive development and there are known cases of women with progeria who had delivered healthy offspring. As for the prevention of heart disease in children with progeria, the next step in research will be to understand the relationship between the lamin A protein and HDL cholesterol levels. Such research, she believes, could have "huge implications for everybody."

ACKNOWLEDGEMENT

The authors are thankful to Mr.Vasanth Kumar PM M.Pharm., (Ph.D)., Assoc. Professor, D.China Babu M.Pharm., (Ph.D)., Asst.Professor, A.Avinash M.Pharm., Asst.Professor, V.Jyothi M.Pharm., B.Kishore Kumar M.Pharm., and thankful to Narayana Pharmacy College, SPSR Nellore Dist., Andhra Pradesh, India for providing the work facilities.

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