ABSTRACT
Progeria, or Hutchinson Gilford Progeria Syndrome, was initially reported by Jonathan Hutchinson in 1886 and further described by Hastings Gilford in 1904. Progeria or Hutchinson–Gilford progeria syndrome is an atypical genetic disorder, usually not inherited. It is characterized by extreme short stature, low body weight, early loss of hair, lipodystrophy, scleroderma, decreased joint mobility, osteolysis, facial features that resemble aged person (premature aging) and accelerated cardiovascular disease. It is almost never passed on from parent to child, as affected children rarely live long enough to have children themselves. Clinical manifestations are evident by the first or second year of life and include the physical characteristics usually associated with the elderly. Classical Hutchinson–Gilford progeria syndrome is usually caused by a sporadic mutation taking place during the early stages of embryo development. Progeria is almost always caused by de novo point mutation in the lamin A gene that activates a cryptic splice donor site, producing a truncated mutant protein termed ‘progerin.’ In the past, doctors had to base a diagnosis of progeria solely on physical symptoms but progeria research foundation establishes the Progeria cell and tissue bank to assist in further research and diagnostic process. Aspirin may help prevent atherothrombotic events, stroke and heart attacks by hindering platelet aggregation. Vitamin supplementation, Fluoride supplements are recommended.

KEYWORDS: Hutchinsons Gilford Progeria Syndrome, progerin, lamin A, premature ageing.

INTRODUCTION
Progeria Syndrome is a rare genetic disorder characterized by dramatic premature aging and accelerated cardiovascular disease.\[1\] The term Progeria is 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 Progeria Syndrome (HGPS).[3]

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. 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] 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).

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. 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.[4, 5]

Symptoms

Children with progeria usually develop the first symptoms during infancy. The earliest symptoms include failure to thrive and a localized scleroderma-like skin condition. As a child ages past infancy, additional conditions usually become apparent around 18–24 months. Limited growth, full-body alopecia, and a distinctive appearance (small face and jaw, pinched nose) are all characteristics of progeria. Signs and symptoms of this progressive disease tend to get worse as the child ages. Later, the condition causes wrinkled skin, atherosclerosis, kidney failure, loss of eyesight, hair loss, 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 hair loss), 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.

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
- Prominent superficial veins

**Skin/Teeth**
- Generalized alopecia
- Delayed and crowded dentition
- 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 sometimes eyelashes
- Dystrophic nails

**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
- Pinched nose, beaked nasal tip
- Faint nasolabial cyanosis
- Thin lips
- Protruding ears; lack of ear lobes

Individuals having most of these features are considered to have the classic HGPS. Individuals with either more or less severe feature are considered to have atypical progeria.[6-8]

---

**Fig. 1** Children with Progeria at different age (top), a healthy cell nucleus (left bottom) and a progeric cell nucleus (right bottom).
CAUSES

Mutation in lamin a causes progeria

Originally thought to be an autosomal-recessive disorder, more recent evidence has identified the genetic basis for progeria to be a single nucleotide mutation with autosomal-dominant expression.\[9-12\]

Lamins are type V intermediate filament proteins and have a short N-terminal "head" domain, an alpha-helical "central rod" domain, and a globular tail domain. Lamins are classified as either A or B type according to their primary sequence, expression pattern, and biochemical properties. B-type lamins are expressed in all cells during development and in adult animals, whereas A-type lamins are expressed in differentiated cells. The LMNA gene encodes three A-type lamins: lamin A (LA), lamin C, and lamin A delta-10. Lamin A contains a C-terminal CAAX box, which undergoes methyl esterification and farnesylation.17 In the process of LA maturation, the C-terminal18 residues, which include the modified C-terminal cysteine, are removed in two specific cleavage steps.

The most frequent LMNA mutation in Hutchinson- Gilford progeria syndrome is a nucleotide substitution at position 1824, C-to-T, resulting in a silent gly-to-gly mutation at codon 608 (G608G) within exon 11 of the LMNA gene. This predicts a deletion of 50 basepairs of prelamin A near the C terminus. Low levels of both the mutant mRNA and the mutant protein, LA delta-50, are expressed in fibroblasts derived from Hutchinson-Gilford progeria syndrome patients.

Table 1: Comparison between a normal cell and a progeria cell

<table>
<thead>
<tr>
<th>STEPS IN NORMAL CELL</th>
<th>STEPS IN PROGERIA CELL</th>
</tr>
</thead>
<tbody>
<tr>
<td>The gene LMNA encodes a protein called prelamin A</td>
<td>The gene LMNA encodes a protein called prelamin A</td>
</tr>
<tr>
<td>Prelamin A has a farnesyl group attached to its end</td>
<td>Prelamin A has a farnesyl group attached to its end</td>
</tr>
<tr>
<td>Farnesyl group is removed from prelamin A</td>
<td>Farnesyl group remains attached to prelamin A</td>
</tr>
<tr>
<td>Normal form called PRELAMIN A</td>
<td>Abnormal form of prelamin A called PROGERIN</td>
</tr>
<tr>
<td>Prelamin A is not anchored to the nuclear rim</td>
<td>Progerin is anchored to the nuclear rim</td>
</tr>
<tr>
<td>Normal state of the nucleus</td>
<td>Abnormally shaped nucleus</td>
</tr>
</tbody>
</table>
DIAGNOSIS

Molecular diagnosis
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.

Clinical diagnosis
Actually there is no clinically approved test to diagnose progeria up to date. In order to diagnose Progeria, doctors observed phenotype i.e., physical symptoms, such as skin changes and a failure to gain weight, which were not fully apparent until a child's first or second year of life, as well as x-rays of patients and urinary hyaluronic acid testing but had no definitive test.

![Fig. 2 Progeria diagnosis and X-ray of progeria patient](image)

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 the measurement is now regarded as unreliable and is not recommended for diagnosis.\textsuperscript{[13]} 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.\textsuperscript{[14]}

**Exams and Tests**

The health care provider will perform a physical exam and order laboratory tests. This may show.

- 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 changes in the gene that causes progeria.

**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.

- **Low-dose aspirin:** A daily dose of aspirin may be recommended to help prevent heart attacks and stroke. Children should only take aspirin under 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.\(^\text{[15]}\)

### NEWER DRUGS

In vitro studies suggest a possible role for the use of Farnesyl Transferase Inhibitors (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 as reversal of the cutaneous manifestations and overall improvement in many of the phenotypic features of progeria, including increased longevity.\(^\text{[16]}\)

Preliminary in vitro studies using transfection of modified oligonucleotides that target the cryptic splice site that occurs in patients with the common 1824C_T mutation have produced encouraging results. By eliminating the production of the mutant LMNA mRNA and protein, normal nuclear morphology is restored, with resultant normalization of heterochromatin structure and gene expression. These nascent studies provide early support for the rationalization of genetic therapy for HGPS patients.\(^\text{[17]}\)
CONCLUSION
Hutchinson Gilford Progeria 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.
REFERENCES
