



Hutchinson-Gilford progeria syndrome (HGPS)

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ABSTRACT

Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare hereditary fatal disease in newborn babies, HGPS is caused by mutations in LMNA that result in the production of an abnormal form of lamin A termed progerin. This genetic disease is very rare that the estimated incidence of HGPS in the USA is one in eight million births, based on the number of cases.

Doctors and researchers say that the cause of death of these children is due to health problem, such as heart problem, veins and strokes. Doctors confirm that premature aging has nothing to do with the death of children with the rare disease (progeria). Currently, researchers and doctors are trying to understand premature aging and determine treatment options. Some areas of research include: Study genes and the course of disease to understand how it develops. This may help identify new treatments. Study of methods of preventing cardiovascular disease.

Keywords:

Hutchinson-Gilford, fatal disease, newborn

Introduction

Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare hereditary fatal disease that affects the skin, musculoskeletal system, and vasculature. HGPS is characterized by clinical features that mimic premature aging, mostly notable in the skin, cardiovascular system, and musculoskeletal systems⁽¹⁾.

The word progeria comes from greek words “pro” meaning “before” or “premature” and “gares” meaning “old age”.

Progeria research has gained momentum particularly in the last two decades because of the possibility of revealing evidences about the ageing process in normal and other pathophysiological conditions.

Various experimental models, both *in vivo* and *in vitro*, have been developed in an effort to understand the cellular and molecular basis of a number of clinically heterogeneous rare genetic disorders that come under the umbrella of progeroid syndromes (PSs).

Although the mutation responsible for this syndrome has been deciphered, the mechanism of its action remains elusive⁽²⁾.

HGPS is caused by mutations in *LMNA* that result in the production of an abnormal form of laminA termed progerin⁽¹⁾.

The child born with this disorder show features of old age from first year of birth and generally dies in teenage⁽³⁾. It is almost never passed on from parent to child⁽⁴⁾.

Or a Medical definition of progeria is rare congenital childhood disorder marked by gross retardation of growth after the first year and by rapid onset of the physical changes typical of old age, usually resulting in death before age 20⁽⁵⁾.

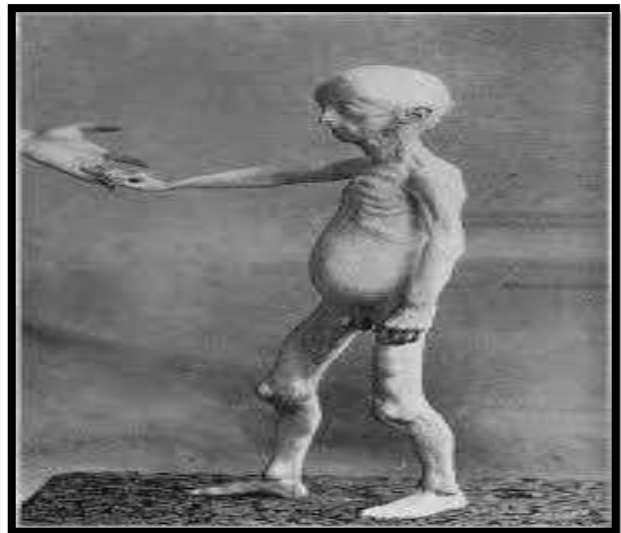
History

In 1886, Jonathan Hutchinson (Figure: 1) reported a case of 3.5 years old boy who had the appearance of an old man. This case of Progeria regarded to be the first case to be described in medical literature under the title (Congenital Absence of Hair and Mammary Glands)⁽⁶⁾.



(Figure .1) : Jonathan Hutchinson.

Hastings Gilford (1897) recognizing the condition as a clinical entity, described a case of his own and re-described Hutchinson's original case (fig2 and 3). He introduced the term Progeria which was taken from the Greek word for old age, "geras". So Progeria means:



PREMATURLY OLD⁽⁶⁾.

(Figure 1): Gilford's case aged 7 years

(figure 3): Adult Gilford

Gilford considered it likely that a description of this syndrome would lead to the more frequent recognition of other cases and that it might be much more common than supposed. This opinion has not been borne out because it's been clear that Progeria still very rare condition.

Because there are atypical cases represent a partial lesion of the same nature, or that in other cases the clinical picture has been modified by the occurrence at a later age period of the pathological processes responsible for progeria, there is a tendency to use this term in connection with other forms of early senility both in children and in adults. But Crooke in (1948) suggest that the title (Progeria) should be reserved for the specific syndrome first described by Hutchinson and Gilford. Gorter (1942) in describing a boy showing some of the signs of Progeria, but lacking others, has suggested that the term (Progeroid) be applied to cases of this type, that of Progeria being reserved for classical cases. Waldorp and del Castillo (1928) had previously suggested the term (Gero-Dystrophic Infantilism) for atypical cases.

In 1950. A case of classical Progeria has been reported by JAMES THOMSON and JOHN O. FORFAR from the Department of Medical Diseases of Children, University of St. Andrews and Royal Infirmary, Dundee. They claim that this is the nineteenth case to be reported since the case of Hutchinson at 1886. And they thought that a dysfunction of the anterior lobe of the pituitary, possibly of the eosinophil cells, is the underlying lesion⁽⁶⁾.

Epidemiology

The estimated incidence of HGPS in the USA is one in eightmillion births, based on the number of cases. Brown suggested that only one half of the affected patients were reported, thereby, the estimated incidence is one in four million live births. Males are affected one and a half times more often than females (M : F = 1.5 : 1). Ninety seven percent (97%) of affected patients are white⁽²⁾. (Presently, there are about 114 children across 39 countries diagnosed with HGPS. The average age of survival is 13.5 years (with life expectancy about 8 - 21 years) and death occurs due to stroke, myocardial infarction, heart failure or atherosclerosis (cardiovascular disease). Of the clinical symptoms of various PSs like growth retardation, skin atrophy, alopecia, lipodystrophy, osteolysis and an augmented susceptibility for malignant tumours, the notable thing in HGPS is that the cognitive abilities remain unaffected⁽⁷⁾.

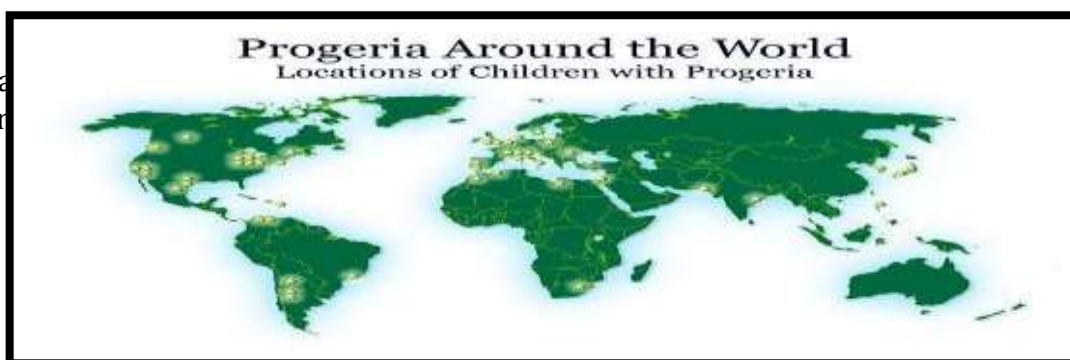
South African the 12-year-old Ontlametse Phalatse, his small girl is one of only 80 children in the world diagnosed with progeria, a premature aging condition. She's also the first black child with the fatal genetic condition. Before Ontlametse celebrated her first birthday "her hair was falling, her nails weren't normal, the skin problems⁽⁸⁾.



(Figure 4): South African Ontlametse Phalatse⁽⁸⁾

Classical HGPS is usually caused by a sporadic autosomal dominant mutation, which means one copy of the altered gene in each cell is sufficient to cause the disorder. The condition results from new mutations in the LMNA gene, and almost always occurs in people with no history of the disorder in their family. There are a few atypical forms of progeria, also called non-classical progeria in which growth is less retarded, scalp hair fall off slowly, progression of lipodystrophy is delayed, osteolysis is more visible with exception in face and survival is observed mostly till adulthood⁴. Non-classical HGPS follows autosomal recessive pattern of inheritance⁽²⁾

cha
syn



phenotypic
progeroid

(Figure 5): show location of children with progeria.

Pathophysiology

HGPS is caused by a mutation in the LMNA gene. The LMNA gene directs the production of lamin A protein and provides structural support for the nucleus. Since LMNA is an autosomal dominant gene, mutations in only one copy of the LMNA gene are sufficient to cause the disease⁽⁹⁾.

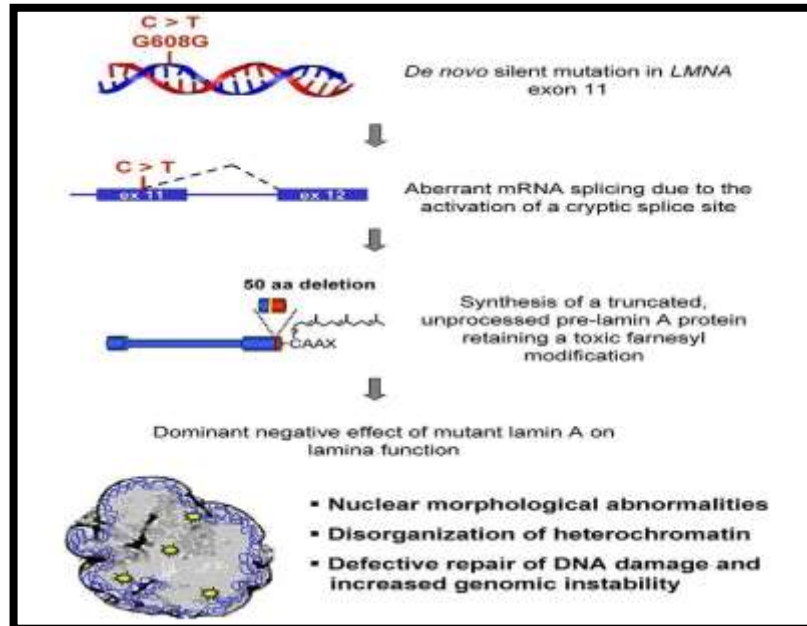
When the LMNA gene is defective (mutated), it produces a protein called progerin that destabilize the cell⁽⁹⁾.

HGPS is caused by C1824T heterozygous mutation of LMNA gene, that is the 1824th base of LMNA gene has a point mutation (C1824T) from cytosine to thymine. Most cases of HGPS are caused by de novo 1824 C T silent mutation in germline cell. This mutation site is located in exon 11 of the LMNA GENE (fig)⁽⁹⁾.

In normal cell, alternative splicing of LMNA transcripts results in two major variant of type A lamin (lamin A and lamin C). lamin A is produced by prelamin A through a series of post translational processing steps⁽⁹⁾.

Mature lamin a is integrated into the nuclear layer, together with lamin B and lamin C, to provide structural support for the nucleus and regulate chromatin structure and gene expression⁽⁹⁾.

In the cells of HGPS patient, the mutation of LMNA gene led to the production of progerin, a variant of prelamin A due to the mutation of LMNA gene. It anchors the inner nuclear membrane, causing the occurrence of HGPS⁽⁹⁾. In HGPS, progerin accumulates in cells, resulting in abnormal nuclear shape, chromatin dysfunction, DNA damage and delayed cell proliferation⁽⁹⁾.

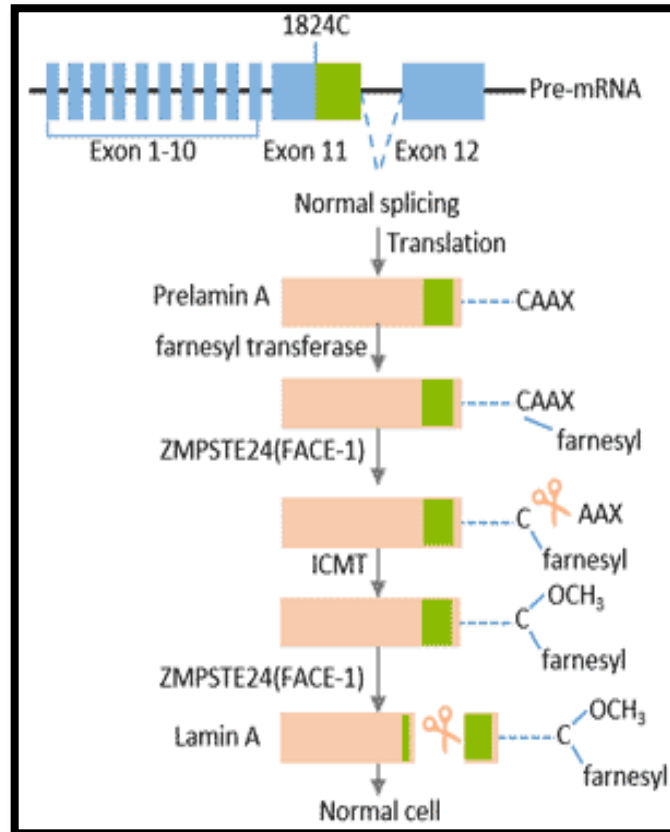


(**Figure 6**): de novo mutation in exon 11 of LMNA gene accounting for molecular basis of HGPS⁽⁹⁾.

How is Progerin Produced?

Normally, lamin A is expressed in the cytoplasm as prelamin A that contain a carboxyl-terminal CAAX motif (C: cysteine, A: aliphatic amino acid, X: methionine or leucine). The cysteine in the CAAX motif undergoes farnesylation. The C-terminal AAX tripeptide is then proteolytically and isopropylcysteine carboxymethyltransferase (ICMT) methylates the farnesylated C-terminal cysteine.

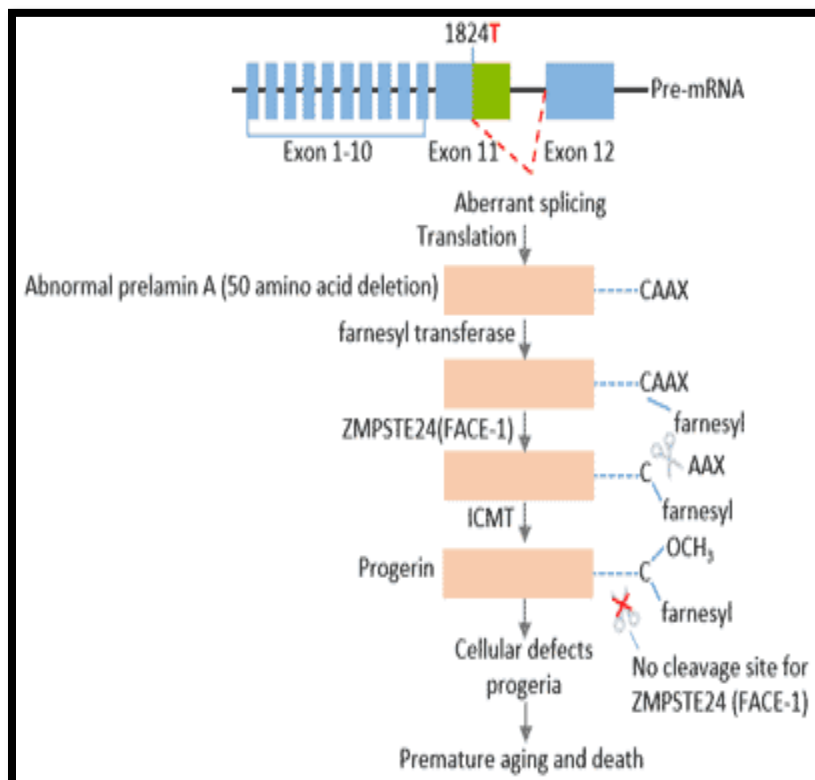
Finally, zinc metalloproteinase ZMPSTE24/FACE-1 removed 15 C-terminal residues that had been farnesylated and carboxymethylated. After being cleaved by protease, prelamin A becomes mature lamin A⁽⁹⁾.



(**Figure 7**): Post translational processing of Lamin A in normal cell

When the LMNA gene is mutated, a splice site of its mRNA precursor is activated, resulting in the deletion of 150 bases of prelamin A mRNA, which ultimately leads to a 50 amino acid deletion near the C-terminus of progerin. Progerin lacks the cleavage site of the protease ZMPSTE24 (FACE1) compared to mature lamin A. Therefore, progerin cannot be cleaved by the protease ZMPSTE24 (FACE1), which allows the farnesyl group at the C-terminus to be retained.

The presence of the farnesyl group causes the progerin to stably bind to the inner nuclear membrane and accumulate, leading to various cellular defects, including abnormal nuclear structure, loss of heterochromatin, DNA repair, and imbalance of redox homeostasis⁽⁹⁾.



(Figure 8): The production of progerin after mutation of LMNA gene

In addition to the LMNA gene, the researchers found that Sun1 is also a specific protein that causes premature aging. When the protein was disrupted, mice lived 2.5 times longer.

Pathology of HGPS

Arteriosclerosis, nephrosclerosis, myocardial fibrosis, and vascular calcifications are significant cardiovascular findings. Necropsy studies on patients with HGPS revealed gross abnormalities in skin, cardiovascular and cerebrovascular tissues, and bones. Loss of subcutaneous fat is always a consistent finding. Recently, magnetic resonance angiography demonstrated bilateral occlusion of internal carotid and vertebral artery origins. Pathological studies have demonstrated premature subintimal fibrosis in the blood vessels.

Skin abnormalities vary according to the site and age of the patient. The epidermis is usually normal to mildly hyperkeratotic, with increased melanin in the basal layer. There is completely disorganized collagen, which is usually thickened and hyalinised. The elastic tissue is surprisingly normal. The density of sweat glands, sebaceous glands, blood vessels, and hair follicles may be normal or reduced.

Skeletal changes are also common. They are short statured. The cranial bones and the diaphysis of the long bones are thin. The clavicles show osteolysis, with replacement by fibrous tissue. Osteoporosis is common. Avascular necrosis of the heads of the femurs and acro-osteolysis of the terminal phalanges are the other dominant bone changes. Delayed and abnormal dentition are also common⁽⁷⁾.

Risk Factors

There are no known factors, such as lifestyle or environmental issues, which increase the risk of having progeria or of giving birth to a child with progeria. Progeria is extremely rare. For parents who have had one child with progeria, the chances of having a second child with progeria are about 2 to 3 percent⁽¹⁰⁾

Clinical features

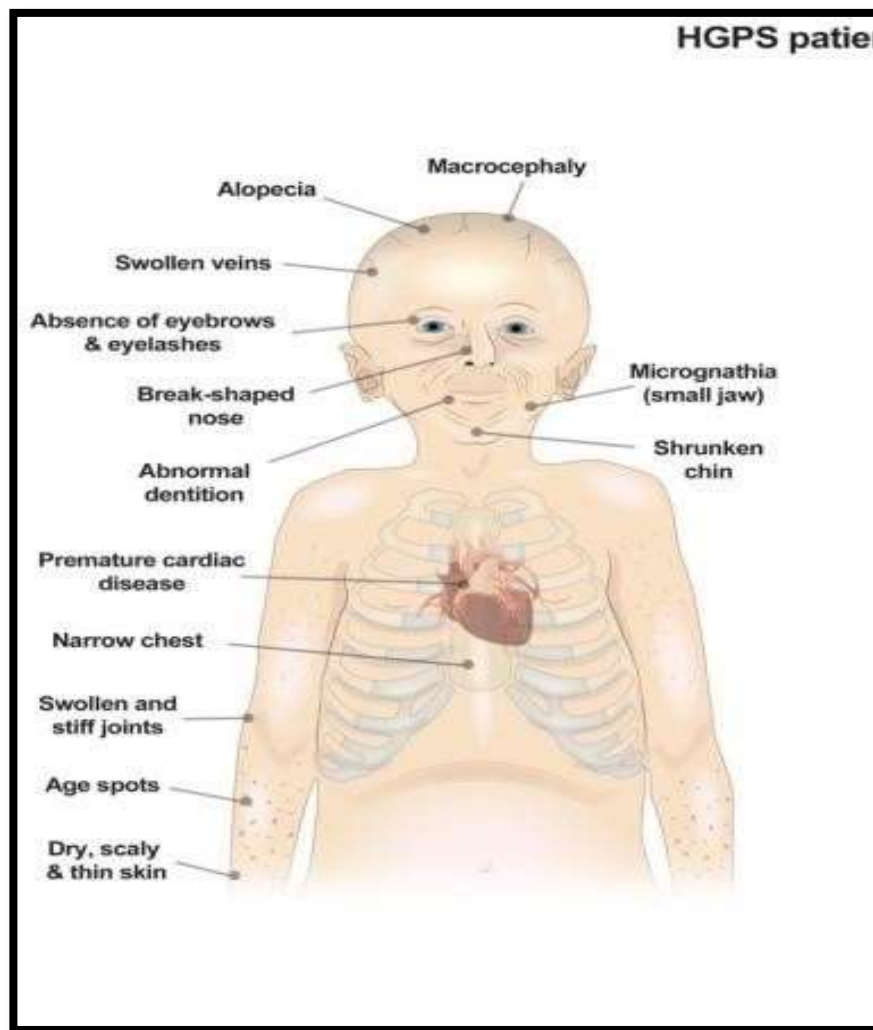
Most children with Progeria are usually born healthy, but they begin to show many signs and symptoms of the disease within the first 2 year of life⁽¹¹⁾.

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

Clinical features of Progeria may include:

- Slowed growth, with below-average height and weight
- Loss of body fat
- Hair loss (alopecia), including eyelashes and eyebrows
- A narrowed face and beaked nose⁸
- Hardening and tightening of skin on trunk and extremities (scleroderma)
- Head disproportionately large for face (macrocephaly)
- Thin lips
- Visible veins
- Prominent eyes
- High-pitched
- Delayed and abnormal tooth formation
- Diminished body fat and muscle
- Stiff joints

- Hip dislocation
- Insulin resistance
- Irregular heartbeat
- Open soft spot (fontanelle)



(Figure 9): summary of physical features and clinical symptoms in patient with Hutchinson-gilford progeria syndrome⁽¹²⁾.

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⁽⁴⁾.

Progeria does not impact child's brain development or intelligence and it does not mean a higher risk of infection. It does not effect motor skills so children with the condition can sit, stand and walk like any other child⁽¹³⁾.



(**Figure 10**): progeria newborn baby.



(Figure 11): A is children with progeria.

B is adult with progeria

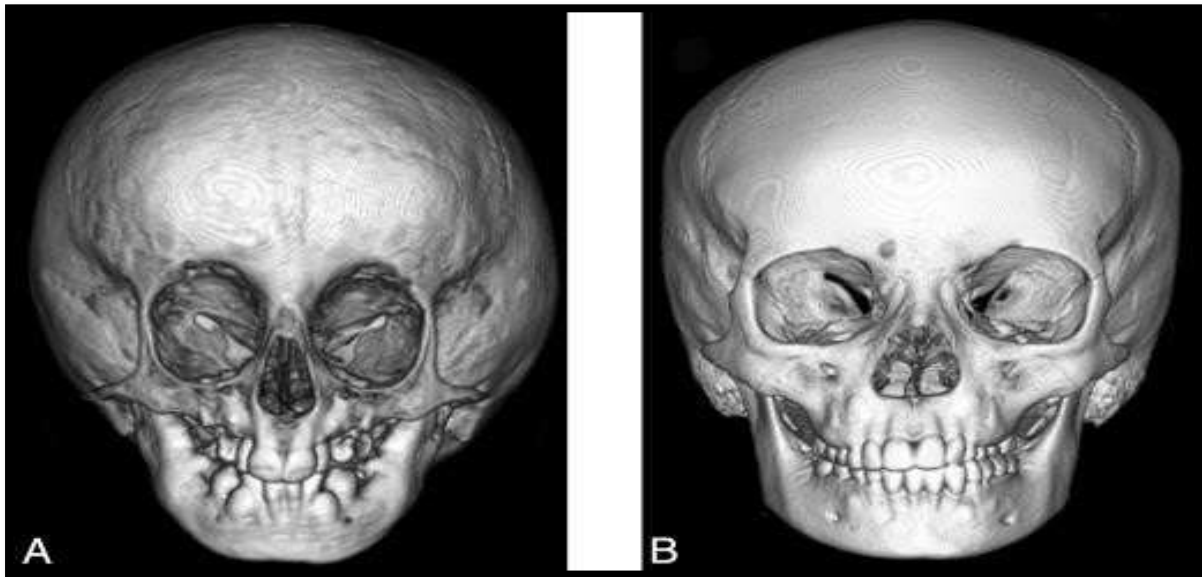
Diagnosis

How is progeria diagnosed?

The gene that causes progeria was identified in 2003, and a genetic test was created that can confirm if a child's symptoms are caused by progeria. The test requires taking a blood sample from the child. (Before this test became available, diagnosis was based on the following⁽¹⁵⁾).

- Characteristic clinical features.
- Classical geriatric disorder of the young.
- Thin, high pitched voice.
- Typical gait.
- Radiography of the skull: craniofacial disproportion, delayed and abnormal dentition.
- Radiography of the hands: radiolucent terminal phalanges.
- Urine test: excessive excretion of the glycosaminoglycan, hyaluronic acid.
- Culture of skin fibroblast exhibited 76.1% DNA repair capacity compared with normal.

- Genetic: sporadic dominant mutation. Arterial biopsy: premature atherosclerosis and subintimal fibrosis⁽¹⁴⁾.



(Figure 12): (A) shows hypotelorism, small mid- and lower face, and disorganized dentition compared with the control (B).

If your doctor has reason to believe your child may have progeria, he or she can contact the Progeria Research Foundation. The foundation's medical director will review the case and can arrange for the test to be done at no cost to families. Results typically come in 2 to 4 weeks⁽¹⁵⁾.

Eligibility

Patients with the classic (G608G) mutation, or other LMNA mutations that result in the same phenotype as that in Hutchinson- Gilford progeria syndrome and approved by the study team, are eligible. All patients also must have a minimum of 1 year of weight measurements that demonstrate a stable slope. They must not have severely impaired liver, kidney, gastrointestinal, or bone marrow function that would prevent them from tolerating the drug⁽¹⁶⁾.

Complications

Children with progeria usually develop severe hardening of the arteries (atherosclerosis). This is a condition in which the walls of the 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 complication 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, cataracts and increased cancer risk typically do not develop as part of the course of progeria⁽¹⁷⁾.

Treatment

There's no cure for progeria, but regular monitoring for heart and blood vessel (cardiovascular) disease may help with managing your child's condition. During medical visits, your child's weight and height is measured and plotted on a chart of normal growth values. Additional regular evaluations, including electrocardiograms and dental, vision and hearing exams, may be recommended by your doctor to check for changes. Certain therapies may ease or delay some of the signs and symptoms. Treatments depend on your child's condition and symptoms⁽¹⁸⁾. These may include:

Low-dose aspirin. A daily dose may help prevent heart attacks and stroke.

- **Other medications.** Depending on your child's condition, the doctor may prescribe other medications, such as statins to lower cholesterol, drugs to lower blood pressure, anticoagulants to help prevent bloodclots, and medications to treat headaches and seizures.
- **Physical and occupational therapy.** These therapies may help with joint stiffness and hip problems to help your child remain active.
- **Nutrition.** Nutritious, high-calorie foods and supplements can help maintain adequate nutrition.
- **Dental care.** Dental problems are common in progeria. Consultation with a pediatric dentist experienced with progeria is recommended⁽¹⁸⁾.

What can parents do to help their family if their child has progeria?

Parents of a child who has progeria should try to create as normal a home life as possible. Try to include the child in as many activities as possible, and be sure to not let other children in the family feel overlooked.

Be honest but age-appropriate with the entire family when discussing the fact that your child with progeria will only live to a certain age. Counseling sessions may be helpful at various times.

Also, talk to your child about the fact that some people will be taken back by seeing him or her, and discuss how your child should respond to stares and whispers⁽¹⁸⁾.

If my child has progeria, will my future children have it? Can a child with progeria attend school?

Progeria is usually does not run in families once a person has had achild with progeria, there is a 2 to 3 percent higher chance of having another child with it because they might have the genetic trait for progeria without actually having the disease.

Many children with progeria attend school, Parents should meet regularly with school administrators, nurses, therapists, teachers and others so that everyone can work together to meet the child's needs. This includes creating and sharing a plan for how to get the child emergency care if needed at school⁽¹⁸⁾.

Case Presentation

Faiq. et al in (2019) found that A 16 year old girl was referred to the rheumatology consultant clinic at Baghdad teaching hospital from the respiratory and chest clinic for evaluation and treatment as a case of juvenile systemic sclerosis with interstitial lung disease, upon seeing the patient, who indeed was suffering from progressive exertional shortness of breath, it was well noticed that she had scleroderma facies with other features including loss of eyelashes and eyebrows, sunken eyes, small chin, protruding teeth and a striking loss of fat all over the body, she had short blunted fingers and toes, kyphotic spine and protruded chest, her skin was thin and pinch-able, and she had prominent forehead veins. These findings alerted us to the possibility that we were dealing with a case of progeria rather than systemic sclerosis⁽¹⁹⁾.

The patient gave history of indigestion with heartburn, poor appetite, constipation, progressive loss of hair, and headaches, she did not have history of joint pain, muscle weakness, skin changes, or Raynaud's phenomenon.

She had her first cycle at the age of 14, and been regular ever since. The teenage was a product of normal vaginal delivery with an uneventful intrauterine life.

she was well at birth but the parents noticed exceptionally worrisome small lips that they have seen before with a similar family member (the patient's cousin) who died at the age of 20.

Her parents share third degree consanguinity, and have 4 children two of them are normal with another 9 year old with the same morphological appearance as our case.

The school performance of the patient was normal till the deformed little fingers were no longer capable of holding the small thin pencil correctly, which along with bullying from peers lead to the joined family and teachers decision to stop schooling at the 2nd primary class.

The girl had a skin and bone appearance, protruding ears, long easily pluckable hair, abnormal gait, thin atrophic stretchable skin, loss of subcutaneous fat around the extremities, mild kyphotic spine, shortened blunted and drum-like digits with preserved nail bed angles, pectus carinatum⁽¹⁹⁾



(Figure 13): The girl had a skin and bone appearance, protruding ears, long easily pluckable hair, abnormal gait, thin atrophic stretchable skin, loss of subcutaneous fat around the extremities, mild kyphotic spine, shortened blunted and drum-like digits with preserved nail bed angles, pectus carinatum.

The patient had mild frontal bossing, a beaked nose, protruding eyes, a high pitched voice, and hypoplastic maxilla and mandible with mild mid facial deformity giving “plucked bird appearance.” Opening of mouth was restricted (interincisal distance 21 mm) and the teeth appeared large, protruded and eroded⁽¹⁹⁾.



(Figure 14): fingurs of progeria



(Figure 15): X-rays of the Patient's hands showing Osteopenia with Acroosteolysis, X-ray of the pelvis showing Coxa Valga.

Based on history and clinical findings, a provisional diagnosis of progeria was made. To confirm the diagnosis, the child was subjected to radiological and biochemical investigations. And diagnosis of PROGERIA put. The patient was put on Domperidone and Statin therapy⁽¹⁹⁾.

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