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Hutchinson-Gilford progeria syndrome - A brief introduction

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Abstract

Progeria is also known as Hutchinson Gilford Progeria Syndrome. It is described by Jonathan Hutchinson and Hasting Gilford. The word Progeria obtained from the Greek word "pro" means "before" and "geras" means "agedness". It is a genetic disorder, not inherited. It is identify by facial appearance containing prominent eye, thin nose, small chin and thin lip. The symptoms of progeria may include alopecia (hair loss), low body weight, decrease joint motility, facial appearance that are similar to old age person and accelerated cardiovascular disease. It is caused due to mutation in LMNA gene in which cysteine is replaced by thymine. This gene is important for producing Lamin A and Lamin C proteins. Treatment includes aspirin may helps to prevent antithrombotic events and cardiovascular disease. Hydrotherapy may be used to improve joint mobility and sign and symptoms of arthritis. FTIs (farnesyl transferase inhibitors) are used to decrease the severity of disease. FTIs are effective by blocking the farnesylation of progerin. Fluoride and vitamin supplements are recommend for progeria patients.

Keywords: Progeria, alopecia, cerebrovascular, mania, Rapamycin.

1. Introduction

The term Progeria obtained from the Greek word "Pro" meaning "prior" or "premature", and "geras", meaning "agedness". Progeria is a rare fatal genetic condition characterized by an appearance of accelerated aging in children. It is found by Dr. Jonathan Hutchinson and Dr. Hasting Gilford. Hence, the state was re-named after them as Hutchinson Gilford Progeria Syndrome (HGPS). [1]

Progeria is caused by mutation in LMNA that produces Lamin A protein that stabilize the nucleus. Lamin A is component of building blocks of the nuclear envelope. It either grows during cell division in a newly conceived child or in the germ cell of one of the parents. [1]

Progeria patient usually enhance the symptoms during first few months of life including wrinkled skin, absence the eye brows and eyelashes, thin lips, a shrunken chin, and a thin nose with a beaked tip. It also causes alopecia (hair loss), short stature, thin/high pitched voice, and pear shape chest region. When a child with progeria is born, they look like any other newborn but over very short period of time, their appearance starts to change. Symptoms usually become visible when the infant is about 12 months old and the life expectancy of children with it is 13 years old. Patient with progeria age 7 times more rapidly than normal. Unlike many other genetic diseases, progeria is not passed down in families. Neither parent is carrier of this genetic information, so the mutation is only in the child's gene. It influences both sexes equally. [2,3]

Many issues can produce from progeria including osteoporosis, heart attack or stroke, malnutrition, cardiac problem, hearing loss, diabetes. Musculoskeletal degradation genesis fatless body, and muscle, stuff joints, hip dislocation, and other symptoms generally off in the non-elderly population.[2,3]

There is no certain test to determine the progeria. Recognize the disease frequently depend upon involvement from the physical appearance of the child with in the first two years of birth. Genetic testing for LMNA mutation can prove the diagnosis of progeria.[4]

There is no effective treatment for progeria and Most of the treatment emphasis on reducing complication

such as heart attack or stroke. Low dose aspirin is used to fight to against atherosclerotic disease. Physical therapy (PT) and occupational therapy (OT) such as hydrotherapy are used to improve joint mobility and symptoms of arthritis. At least 90% children with progeria die from heart attack or stroke. There are approx 200-250 children living with progeria at a given time.[4]

1.1 Progeria

Progeria syndrome is an extremely very genetic disorder which affects skin, musculoskeletal system and blood vessels. The term Progeria obtained from the Greek word "Pro" meaning "prior" or "before", and "geras", meaning "oldness". It is discovered by Dr. Johanthan Hutchinson in 1886 and Dr. Hasting Gilford in 1897. Hence, the state was re-named after them as Hutchinson Gilford Progeria Syndrome (HGPS). [5] Progeria is a condition in which the body of child ages fast. This is a genetic condition and can affect any gender. This is not inherited. In this condition, progeria protein is made by certain gene. This abnormal protein causes the child to grow old quickly. This sign of progeria may appear during the first year of the child. Progeria is the result of point mutation in the Lamin A gene, where cytosine is exchange with thymine. Progeria children grow 4-7 times faster than normal. They will look normal at birth until early age then begin to stop developing overtime they begin to look like an older person. The physical features of child with progeria include a bigger head, big eyes, small lower jaw, and ear with stick out, visible vein, slow tooth growth, high pitch voice, whole body alopecia and loss of subcutaneous fat. Progeria does not affect the children mentally to all. The average life span of progeria patient is 13 years. Only 18 children in the united states are suffering from progeria.[6]

2. Epidemiology

HGPS is a very infrequent disorder found to be 1 in 4-8 million births. It influences both sexes equally. There are approximately 200-250 children living with progeria at a given time. Progeria is normally produced by irregular mutation takes place during the early stage of embryo development. It is virtually never passed on from affected parent to children. Progeria affected children have no contrast in weight and they look just like any other baby, but over very short period of time their appearance starts to change. Most of the progeria affected children die due to myocardial infraction and heart attack or stroke. According to the Progeria Research Foundation (PRF) report 134 progeria patient were detected in Dec 2015. The maximum life span is not more than 13.5 years.[4,7]

Figure 1: Occurrence of progeria children around the world as of Dec-2015.[7]

2.1 Causes

Hutchinson-Gilford Progeria Syndrome is caused due to mutation in the LMNA gene in which cystein is replaced by thymine. For structural protein, LMNA gene codes known as Prelamin A. Lamin are a one type of V median filament protein. Lamin has short N- terminal "head" domain, "central rod" domain, and "globular tail" domain. Lamin are classified as-

- A type lamin
- B type lamin

A type lamin is associated with differentiated cells while B type lamin is associated to all cells during

development and in adult animal. LMNA gene indicates 3 A type lamins-

- Lamin A
- Lamin C
- Lamin A delta- 10

Prelamin A consist CAAX box at C- terminal which undertake fernesylation and permit to bind membrane, individually the nuclear membrane. After Lamin gene has been restrain to the nuclear membrane, C-terminal contains fernesylated cysteine is break by a precise protease. The develop protein is currently Lamin A and follow up work interior the nucleus. In progeria disease, the identification area that the enzyme needs for breakdown. Lamin A is not grow while prelamin A grows on the nuclear membrane and cause nuclear blister resulting in sign and symptoms of progeria.[8-10]

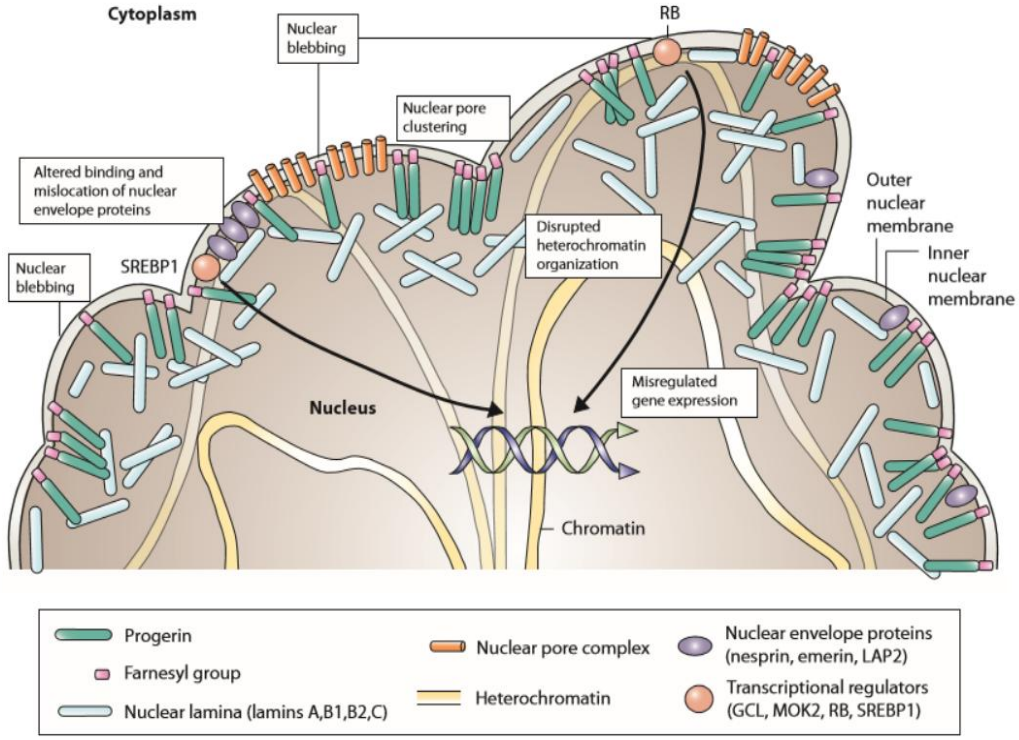

Figure 2: Structural and functional consequences due to the improper embedding of lamin A protein in the nuclear lamina.[9,10]

2.2 Symptoms

HGPS patient are looking healthy at birth until early age then begin to stop developing overtime they begin to look like an older person. Children with progeria are shorter than normal children. Progeria children usually develop the first symptoms during their first few month of life. The earlier symptoms may includes-

- Limited growth
- Failure to thrive (height & weight) and a localized scleroderma like skin condition.
- Loss of subcutaneous fat
- Whole body alopecia
- Absence of eyebrows and eyelashes
- Beaked shaped nose
- Shrunken chin
- Short stature
- Small face
- Big eyes
- Stiffness of joints
- Fine lips and limbs
- Small lower jaw ear with stick out
- Swollen vein
- Pear shape chest region
- Thin/High pitch voice
- Hearing loss
- Wrinkled skin as like older people
- Abnormal heart beat
- Premature cardiac disease
- Age spots
- Asymmetrical tooth formation
- High blood glucose and cholesterol level
- Hair follicles are not present
- Sebaceous gland absent

Progeria does not affect the children mentally to all.[10-12]

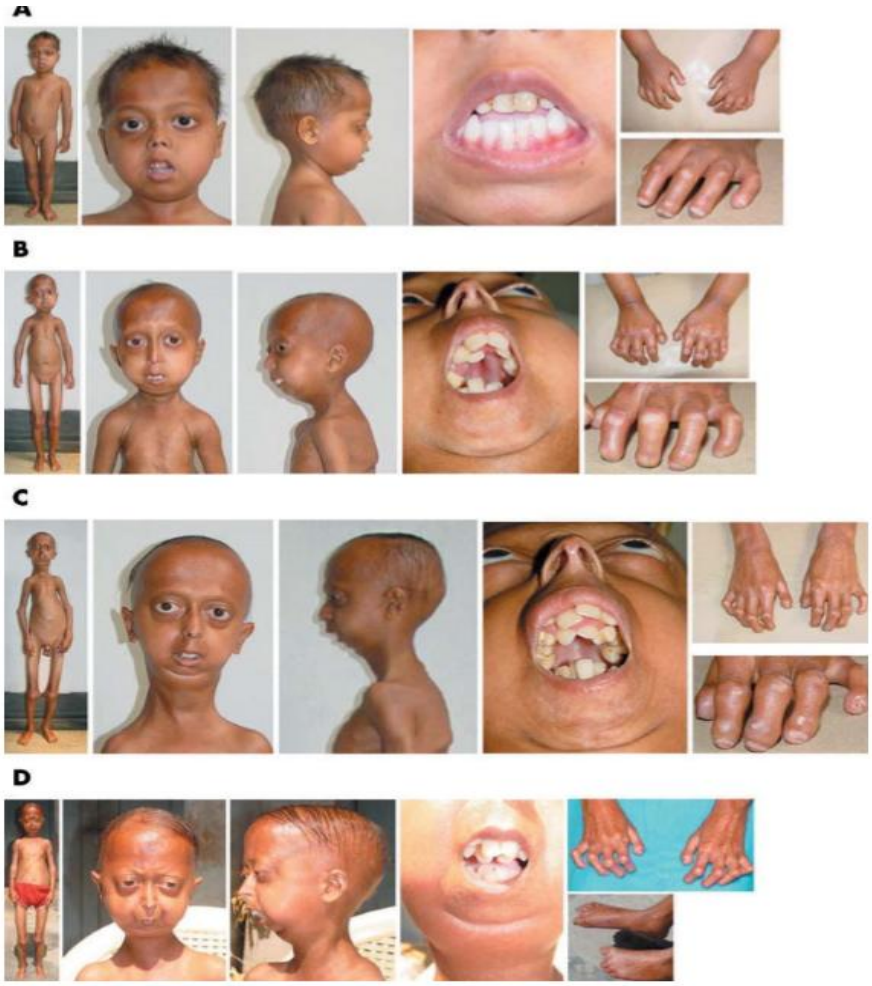

Figure 3: Clinical features observed in HGPS children.[11-13]

2.3 Diagnosis

Diagnosis is based on sign and symptoms, such as -Skin problem, Alopecia, Irregular growth [14]

2.4 Clinical diagnosis

The diagnosis of progeria is proved by genetic test for lamin A gene mutation. The most common typical symptoms are failure to thrive (55%), and alopecia (40%), skin problem (28%), and lipodystrophy (20%) which can be used for diagnosis. For diagnosis of progeria, the mean age was 2.9 year in literature case (data obtained on 72 HGPS patient).[15]

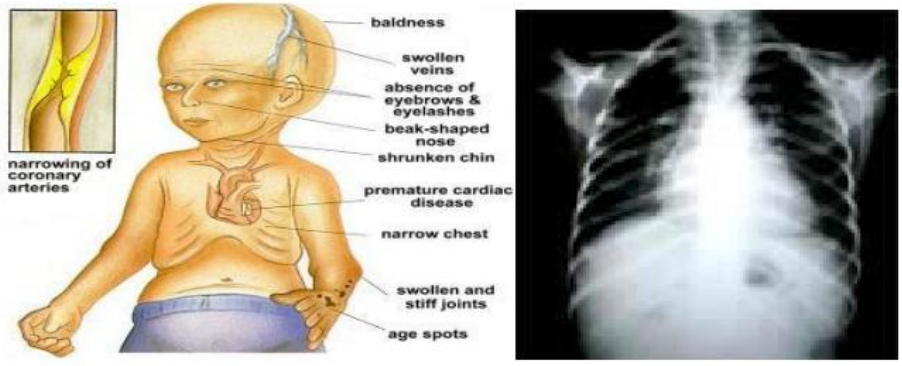

Figure 4: Progeria diagnosis [16]

2.4.1 Urinary hyaluronic acid testing

Increased testing of hyaluronic acid has been observed in HGPS patient, who is important for sclerodermatous and it is not approved for diagnosis. HGPS shows a dose of aspirin for their lives because it helps to stop atherothrombic events and cardiac attack by platelets accumulation. Now, there is no treatment for the disease.[14,16]

Exam and tests

The health care supplier gives will conduct a laboratory tests and physical exam. This may shows-

- Lowering the level of blood sugar
- Abnormal skin change

Heart attack testing may shows sign of atherosclerosis of blood vessels. Genetic test can observed change in lamin gene which cause progeria.[16]

2.5 Treatment

Currently, no effective treatment for HGPS (Hutchinson-gilford progeria syndrome). The careful study for cerebrovascular and cardiovascular is necessary. Low dose aspirin is used to reducing complications (such as cardiovascular disease). Morpholinos is used to reduce progerin production.

➢ **Aspirin**

Low dose aspirin is used to prevent the cardiovascular and cerebrovascular disease. Aspirin should take under healthcare professional because it shows many serious side effects.

➢ **Physical and occupational therapy**

Physical and occupational therapy can be used to support physical activity and child remains active. Hydrotherapy may be used to improve joint mobility and reduced the sign and symptoms of arthritis.

➢ **High calorie dietary supplement**

High calorie diet may be used to prevent weight loss. Supplements should be taken under the healthcare professional.

➢ **Feeding tube**

Feeding tube is used for infants who have difficulty feeding due to physical problems.[9,15-17]

New Drugs

Farnesyl transferase inhibitors (FTIs), Aminobisphosphonates and statins

Newly drug, which are used to treat cancer and may also treat HGPS in the future called, farnesyl transferase inhibitors (FTIs). The effective use of this therapy is to decrease the need of energy and to increase the weight and height of progeria patient. FTIs are used to decrease the severity of disease. These drug are effective by blocking the farnesylation of progerin. It blocks the farnesyl protein transferase which directly acts on farnesylation of prelamin A consist of C- terminal CAAX- box. Farnesyltransferase inhibitors prevent the activity of an enzyme required to make a relationship between progerin protein and farnesyl groups. This relationship makes a indefinite addition of the progeria to the nuclear rim. Farnesyl protein transferase is absent, Prelamin-A is managed by the geranylgeranylation. Therefore Progerin levels are increased, thus the potency of FTIs in the treatment is decreased. This alternation could be inhibited by blocking the creation of both geranyl-geranyl and farnesyl precursors by aminobisphosphonates and statins. Lonafarnib is a farnesylated blocker which can avoid this relationship, so progerin can not added to the nuclear rim and it shows normal state. [7,14,15,18,19]

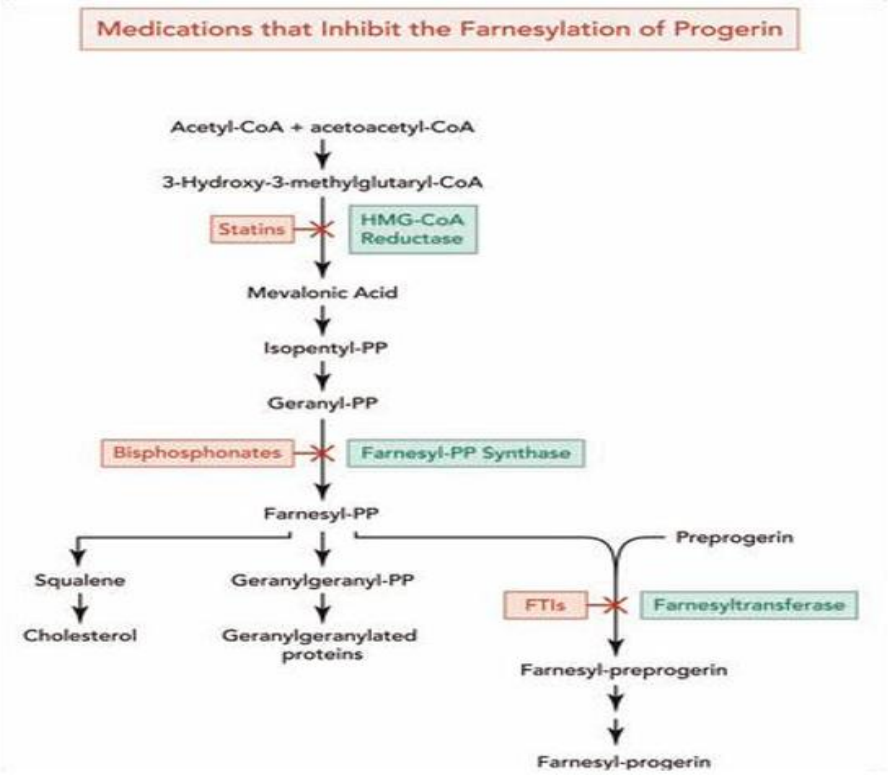

Figure 5: FTIs and Statins for the treatment of HGPS[7,19]

Rapamycin

Rapamycin, also known as "Sirolimus". Rapamycin is used to block the growth of structural defect in the nucleus and enhance the lifespan of affected cells. It also inhibits the atherosclerosis. Rapamycin can be administered to progeria patient because it needs blood draws to determine the levels of drugs. While FTIs may prevent the progerin from growth whereas injurious progerin is evacuated from cell by the rapamycin action.[7,17]

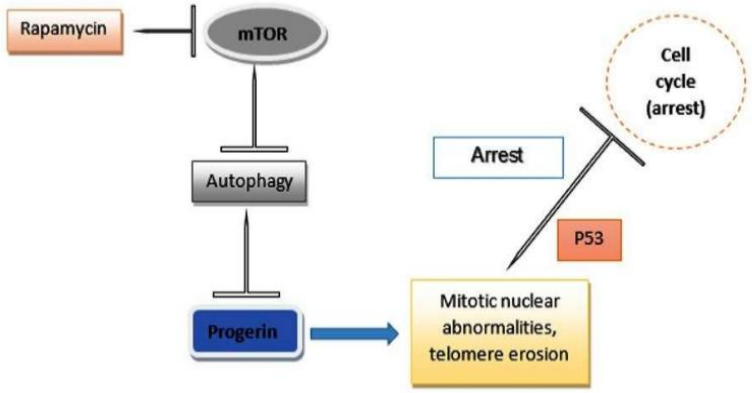

Figure 6: Rapamycin inhibits telomere erosion and cell cycle by decreasing the progerin levels.[7,19]

3. Conclusion

Progeria is a ultra rare premature agedness disease. Alopecia (hair loss), thin lip, prominent eye, and small chin are the main symptoms of progeria. This study gives a vigrous untreated survival profile which can be used for comparison current and in the later to assess changes in survival with study for progeria. The now comparison determining increase survival with farnesylation inhibitors gives the first confirmation of study for this ultra rare segment premature aging disease. Further more research will probably determine this contradiction.

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