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Hutchinson– Gilford Progeria Syndrome: A Review

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ABSTRACT

Hutchinson– Gilford Progeria Syndrome is a very rare disorder characterized by premature ageing caused due to mutation in LMNA gene. The child born with this disorder shows features of old age from first year of birth and generally dies in teenage. The clinical symptoms include alopecia, thin skin, stiffness of joints etc. All of the children suffering from this disease appear identical. The pathophysiology of disease is not very clearly understood. Various methods for diagnosis are being developed and clinical trials on some drugs that may be used in treatment are being carried out. The aim of present review is to understand the various aspects of disease with special emphasis on pathophysiology, symptoms, recent trend in treatment and future opportunities.

Key words: Lamin A; FTI; HGPS; premature ageing.

INTRODUCTION

Hutchinson– Gilford Progeria Syndrome is a rare, sporadic, autosomal dominant, fatal childhood disease first described by Dr Jonathan Hutchinson in 1886[1, 2, 3]. Dr. Hastings Gilford reported similar clinical findings and named the condition as Program [4, 5]. The term Progeria is derived from the Greek word geras, meaning old age and Latin meaning of Progeria is being prematurely old. The disease involves premature aging, generally leading to death due to myocardial infarction or stroke [6]. The disorder has a very low incidence and occurs in one per four million live births [7]. Those born with Progeria typically live about thirteen years, although many have been known to live into their late teens and early twenties [8, 9]. Very rare individuals may even

reach their forties. It is a genetic condition that occurs as a new mutation in one gene and is not usually inherited, although there is a uniquely inheritable form [10]. The aging process of body accelerates much faster than what it does in normal humans.

A study that compared HGPS patient cells with the skin cells from LMNA young and elderly human subjects found similar defects in the HGPS and elderly cells, including down-regulation of certain nuclear proteins, increased DNA damage, and demethylation of histone, leading to reduced heterochromatin [11]. Children with Progeria appear normal at birth while the symptoms manifests in first or second year of life when skin changes, failure to gain weight, alopecia etc occurs [12].

Fig. 1: Children suffering from Progeria

Death is due to complications like atherosclerosis, myocardial infarction, congestive cardiac failure or coronary thrombosis. The causes and manifestation of Progeria are not very clear [13]. Although being rarest of disease it may teach about the mechanism of ageing. Identification of the gene responsible for HGPS provides an explanation for rarity of the condition [14]. The various parameters like growth hormone, thyroid and parathyroid functions, pituitary and adrenal glands are found to be normal while there may be accelerated metabolic rate. A low degree of insulin resistance has been reported in certain cases. Abnormality in skin may be attributed to elevated elastin and collagen type IV production [15]. Scientists are particularly interested in Progeria as it might reveal the clues about normal ageing process [14, 16].

Epidemiology:

HGPS is a very rare disorder prevalent in 1 in four million births. Currently there are 35-45 known cases in the whole world[7]. Since 1886 approximately 100 cases have been identified around the world [17]. 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 [14]. 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.

Pathophysiology:

The major symptoms in the patient with HGPS occur due to mutation in the gene LMNA. The gene, LMNA, located on band 1q21.1-1q21.3, encodes Lamin A, which is a type V intermediate filament protein that localizes to the cell nucleus and forms the nuclear lamina inside the nuclear membrane [18]. De novo mutations associated with advanced paternal age are responsible for most cases. Lamin A and Lamin C, two abundant structural proteins of the nuclear lamina, are products of the same gene, LMNA. Lamin A is twelve exon protein. Prelamin A, the precursor of Lamin A, involves the splicing from middle of exon 10 to exon 11 then to exon 12 [19]. Prelamin A has CAAX as terminal amino acids. This terminal triggers farnesylation of the carboxy terminal cysteine (the C of the CAAX tetrapeptide) by a cytosolic enzyme, known as protein farnesyltransferase. The farnesylated Prelamin A attaches with the Endoplasmic Reticulum. After farnesylation, the last three amino acids of Prelamin A are cleaved by an endoprotease. The enzymes responsible for release of these amino acids are: a Zinc metalloprotein ZMPSTE24 and a prenyl protein endopeptidase RCE1 [20, 21]. After the release of the terminal amino acids, farnesyl-cystein residue is methylated by an enzyme Isoprenylcystein Carboxy Methyl Transferase (ICMT) [22, 23]. In the last step of normal Lamin A synthesis, the end 15 amino acids of Prelamin A including farnesylcystein methyl ester are released off by ZMPSTE24 and mature Lamin A is released from endoplasmic reticulum into cytosol. The resulting protein, now Lamin A, is no longer membrane-bound, and carries out functions inside the nucleus [24, 25].

In the diseased person there is mutation in one allele of the LMNA gene. Approximately 90% of patients with the syndrome have an identical mutation in one allele of the gene, consisting of a C-to-T substitution at nucleotide 1824 (1824 C→T) [24]. The disorder is rare because affected people die before reproductive age, so every case represents a new mutation, and the mutation needs to be precisely targeted to produce the phenotype. The LMNA mutation at position 1824 does not change the amino acid of the corresponding codon in the messenger RNA (mRNA). But it causes defective mRNA splicing by activating a cryptic splice donor in exon 11, resulting in a synthesis of abnormal protein named “Progerin,” with an internal deficiency of 150 bases i.e. 50 amino acids as compared with normal Lamin A. The defective splicing caused by 1824 C→T mutation deletes the part of protein that is targeted by ZMPSTE24 at the release step [26]. This leads the defective Progerin to remain farnesylated and membrane bound. The Progerin thus formed enters the nucleus by diffusion through endoplasmic reticulum. The prolonged binding of Progerin to nuclear membrane disrupts the nuclear lamina causing blebbing of nuclear membrane which leads to abnormal binding of chromatin to nuclear envelope [27, 28]. The relation of above sequence of reactions with clinical features of Hutchinson– Gilford Progeria syndrome in not very clearly understood yet. The abnormal nuclear membrane may be more prone to mechanical damage leading to increased cell death. The disturbed binding of chromatin to nuclear membrane may lead to abnormal gene expression. Also the defected nuclear lamina may affect the normal DNA repair mechanism [27].

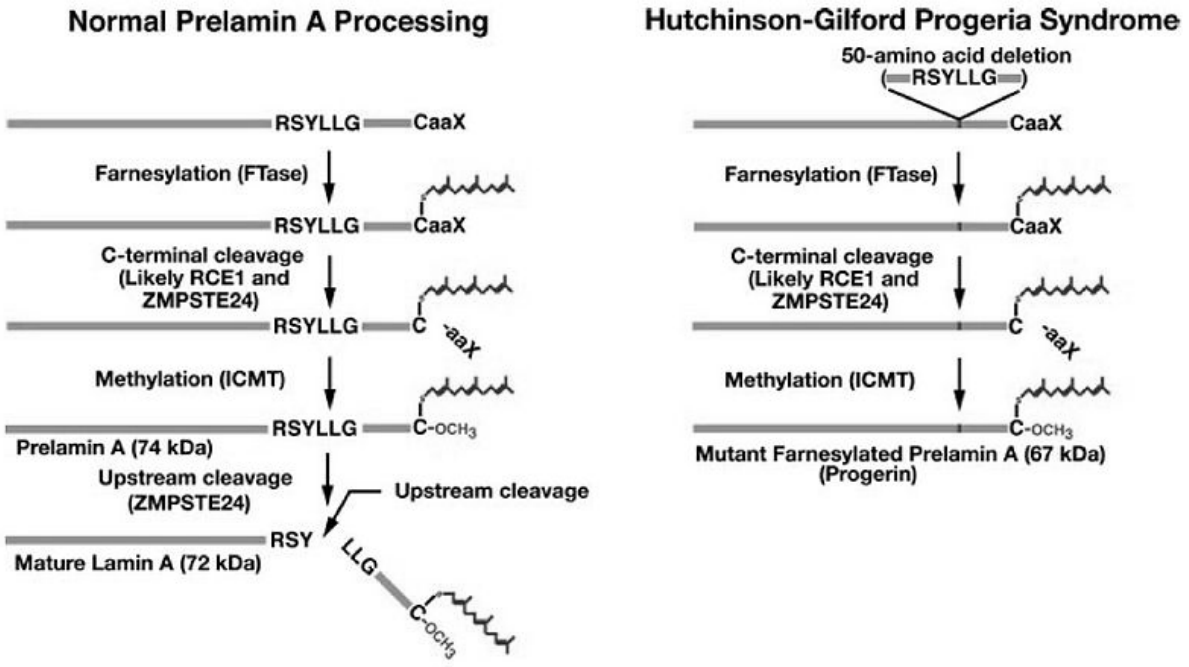

Fig. 2:Biogenesis of lamin A in normal cells and the failure to generate mature lamin A in HGPS.

A characteristic finding in persons with Progeria is an increase in hyaluronic acid excretion. In addition to persons with Progeria, it is only detected in those with Werner syndrome, a disease characterized by a later onset of premature aging that occurs during the second decade of life. Usually, hyaluronic acid and other glycosaminoglycan production increases during the fifth to seventh decades of life. Possibly, the increase in hyaluronic acid is a normal feature of advancing age. Fibroblasts from patients with Progeria show a 3-fold increase in total glycosaminoglycan production and, in particular, hyaluronic acid production, compared with age-matched control groups. This increase results from an abnormality in degradation and is not caused by increased synthesis. Hyaluronic acid is also necessary for the morphologic development of blood vessels. A reduction or absence of blood vessels is noted in regions of high hyaluronic acid levels. The decreased density of vasculature, sclerodermatous changes in the skin, and the high prevalence of cardiovascular disease present in persons with Progeria may be induced by increased hyaluronic acid levels. Increased hyaluronic acid levels may also promote calcification of blood vessels, thus contributing to arteriosclerosis [29].

Clinical Manifestations:

The earliest symptoms include failure to thrive and a localized scleroderma-like skin condition. As a child ages past infancy, additional conditions become apparent. Limited growth, alopecia, and a distinctive appearance (small face and jaw, pinched nose) are all characteristic of Program [1, 6]. The characteristic clinical findings of Hutchinson-Gilford Progeria syndrome (HGPS) include abnormalities of the skin and hair in addition with characteristic facial features and skeletal abnormalities[1]. Delayed, abnormal dentition is also common. People diagnosed with this disorder usually have small, fragile bodies, like those of elderly people. Later, the condition causes wrinkled skin, atherosclerosis, and cardiovascular problems [5]. Mental

development is not affected. The development of symptoms is comparable to aging at a rate eight to ten times faster than normal, although certain age-related conditions do not occur. Specifically, patients show no neurodegeneration or cancer predisposition [16]. They do not develop physically mediated "wear and tear" conditions commonly associated with aging, like cataracts (caused by UV exposure) and osteoarthritis (caused by mechanical wear) [30]. The following are other clinical symptoms:

Skin and hair:

- Skin changes at the time of birth may be present. The major abnormalities include shiny and in elastic skin. The skin may appear wrinkled with low cutaneous fat. The patient is physically weak. When in contact with bright sun light, hyper pigmentation of skin may occur with irritation. Complete loss of hair of all the body parts including scalp, eye lash and skin [7].

Musculoskeletal abnormalities:

- The limbs are thin with low muscular mass. The joints appear prominent. There may be flexion of knee joint leading to disturbed gait. The patient walks a bit abnormally. The thoracic cage becomes pear shaped. Face appears like aged person, with prominent eyes and ears slightly bigger in size. Inscissors fall at early age.

Other reported abnormalities:

- The voice has high pitch. Scars may be present over the body. Weight to height ratio is low. The nails may appear dystrophic. The patient generally suffers from hypertension. Difficulty in hearing or even complete loss may accompany. Osteoporosis is major feature with weak bones. The patient is prone to fractures. There may be complete loss of appetite. Delayed teeth growth or loss of teeth is prominent clinical feature. The prothrombin time is prolonged with elevated platelet count. The serum level of phosphorus increases and that of calcium decreases.

Emotionally, patients with HGPS have the feelings similar to that of age-matched healthy persons. They express proper mood and affection [31]. They may have particular affection for someone like mother or father. Patients with HGPS are aware of their different appearance as compared to others. They have tendency to keep away from strangers. They show good social interaction with friends. Intelligence of the patients is normal.

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.

- Cardiovascular complications include myocardial infarction and congestive heart failure. The reason of death in most of the cases is 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.
- The other causes of death may include marasmus, loss of mobility or weakness.

Diagnosis:
The diagnosis of disease depends upon proper interpretation of clinical and radiological findings. The characteristic radiological findings include abnormalities in skull, thoracic cage, long bones and phalanges [31]. Acroosteolysis is the earliest abnormal finding, and joint contracture preceded the development of coxa valga. The cranial bones tend to be hypoplastic and fontanels become open and longer than expected. The presence of wormian bones is common. Narrowing of posterior ribs is frequent with thinning of distal clavicles. The loss of bones of fingers and toes are major abnormalities associated with progression of disease. Elevated levels of hyaluronic acid are seen in urine. Brain magnetic resonance angiography may identify cerebrovascular occlusive disease. ECG and echocardiography should be performed to monitor coronary artery disease and congestive heart failure.

Treatment:
No treatments have been proven effective. Most treatment focuses on reducing complications (such as cardiovascular disease) with heart bypass surgery or low-dose aspirin. Children may also benefit from a high-calorie diet. Growth hormone treatment has been attempted [30]. Whatever the pathophysiologic process, knowledge of the molecular defect in Hutchinson–Gilford Progeria syndrome has suggested possible therapeutic approaches. It appears that Progerin, which is persistently bound by farnesylation to the nuclear membrane, is toxic. It has been hypothesized that interference with farnesylation might reduce this toxicity. This might be accomplished by interfering with production of the farnesyl group or by blocking the farnesylation reaction. A type of anticancer drug, the farnesyltransferase inhibitors (FTIs), has been proposed, but their use has been mostly limited to animal models [32, 33]. A Phase II clinical trial using the FTI Lonafarnib began on 7th May 2007 in Children's Hospital, Boston. This was the first ever clinical trial carried out in the history of this disease. The trial started with twenty eight children from sixteen different countries with age 3 to 15 years. For the purpose

each of the children have to travel to Boston every four months for periodic check up and to receive new drug and stay in Children's Hospital for 4-8 days. The estimated expense for the trial was $2 million. The particular interest of the scientists during the clinical trial are the rate of growth, levels of prelamin A, Lamin A, Progerin etc. the researchers will also find the leptin levels, glucose utilization, hearing loss, skeletal and dental abnormalities. The trial was expected to complete in December 2009. The resuls are expected to be published soon.

The farnesyl group is synthesized through the cholesterol biosynthetic pathway, and drugs such as statins and bisphosphonates are known to reduce its production. Farnesyl transferase inhibitors have been developed because of the role of farnesylation in the function of ras, an oncoprotein involved in many forms of cancer [34]. Such agents have been shown to diminish the nuclear blebbing of cells from patients with Hutchinson– Gilford Progeria syndrome in vitro and to ameliorate a Hutchinson– Gilford–like phenotype. Although there are side effects, children with cancer who have been treated with farnesyl transferase inhibitors have an acceptable side-effect profile. Other therapeutic approaches to Hutchinson–Gilford Progeria syndrome that have been considered are the use of small RNA molecules to inhibit Lamin A production (RNA interference) and oligonucleotides that bind to the mutant splice donor to inhibit the abnormal splicing event [35].

Lonafarnib is an FTI (Farnesyltransferase inhibitor), a drug that can reverse an abnormality in Program cells in the laboratory, and has improved disease in Progeric mice.

Researchers have identified two additional drugs that, when used in combination with the current FTI drug being tested, may provide an even more effective treatment for children with Progeria than FTI's alone. These are Pravastatin and Zoledronic acid. Pravastatin is a member of the drug class of statins. It is usually used for lowering cholesterol and preventing cardiovascular diseases [36]. Zoledronic acid is a

bisphosphonate, usually used as a bone drug for improving osteoporosis, and to prevent skeletal fractures in people suffering from some forms of cancer. All of these three drugs block the production of farnesyl molecule that is needed for Progerin to create disease in Progeria.

Supportive Therapies:
Hydrotherapy- Hydrotherapy promotes relaxation, relieves pain, assists movement and enables exercise. It can also help prevent arthritis from getting worse.

Nutrini- Patients have a very small appetite and don't really enjoy eating. Nutrini provides all of the nutrients essential for well-being and health.

Pro-Cal- Pro-Cal is a new generation protein and calorie food that can be added to a wide variety of food and drink to enrich the energy and protein content of the normal diet with the minimum effect on taste, volume and texture.

Vitamin E- Vitamin E is a fat-soluble vitamin that protects Vitamin A and essential fatty acids from oxidation in the body cells and prevents breakdown of body tissues. Antioxidants such as Vitamin E act to protect the cells against the effects of free radicals, which are potentially damaging by-products of the body's metabolism. Free radicals can cause cell damage that may contribute to the development of cardiovascular disease and cancer.

Aspirin- Aspirin is now accepted as an important weapon in the prevention of heart disease. Recent clinical trials have shown that aspirin reduces the risk of strokes and heart attacks. A small dose of aspirin is enough to prevent dangerous blood clotting. This is of benefit to people with narrowed coronary arteries which is common place in children with Progeria

Fluoride- All Program children have problems with their teeth. Underdevelopment of the facial bones and the lower jaw leads to delayed eruption of the teeth, they can be small, irregularly formed or even missing and tooth decay is common. Fluoride can greatly help dental health by strengthening the tooth enamel, making it more resistant to tooth decay.

CONCLUSION

Hutchinson– Gilford Progeria syndrome is a disease which has been a subject of curiosity among the scientists. The research is being carried out worldwide to understand the underlying cause of the disorder. Although the mutation in LMNA gene is responsible, the exact mechanism is not

yet very clear. Due to the rarity of the disease it becomes rather difficult to carry out clinical research on the drugs. Currently Farnesyltransferase Inhibitors (FTIs) are being looked upon as potential drug treatment for the disease. Lonafarnib is undergoing Phase II clinical trial. Until specific drug treatment is discovered, the supportive therapies like Growth Hormone, Aspirins etc along with various measures to prevent the complications of the disease may prove useful in prolonging the life to some extent.

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