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A REVIEW ON HUTCHINSON-GILFORD SYNDROME

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ABSTRACT

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. The disorder has a very low incidence and occurs in one per four million live births. Those born with Progeria typically live about thirteen years, although many have been known to live into their late teens and early twenties. Progeria shows characteristic facial appearance including prominent eyes, thin nose with a beaked tip, thin lips, a small chin, and protruding ears, severe hardening of the arteries beginning in childhood. The main clinical and radiological features include alopecia, thin skin hypoplasia of nails, loss of subcutaneous fat, and osteolysis. Intelligence is not impaired. Early death is caused by atherosclerosis. Transmission is most likely from a sporadic autosomal dominant mutation. Clinical manifestations are evident by the first or second year of life and include the physical characteristics usually associated with the elderly. Mentally, patients are alert and attentive with normal intelligence and emotions. Histopathologic changes occur primarily in the skin, bone, and cardiovascular tissues, while other organs appear to be unaffected. Laboratory findings are unremarkable, with the exception of an increased urinary excretion of hyaluronic acid. Death results from cardiovascular abnormalities in the majority of cases and usually occurs between the ages of 10 and 15 years.

Keywords: Hutchinson-Gilford Progeria Syndrome, Premature ageing, Premature senility syndrome, HGPS.

INTRODUCTION

Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare hereditary disease that affects the skin, musculoskeletal system, and vasculature. HGPS is characterized by signs of premature aging. The term progeria is derived from the Greek word *geras*, meaning old age. Significant morbidity and mortality result from accelerated atherosclerosis of the carotid and coronary arteries, leading to premature death during the first or second decade of life.

Progeria also known as Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare genetic disorder that affects the children and gives them an appearance of accelerated aging. HGPS is caused by a de novo point mutation in the lamin A gene (LMNA) that activates a cryptic splice donor site, producing a truncated mutant protein termed ‘‘progerin’’. Lamin A is a key protein within the nuclear lamina, an Intermediate filament meshwork lining the inner nuclear membrane that provides structural support for the nucleus. The word Progeria comes from the Greek “progeros” meaning prematurely old (“pro” means before and “geras” means old age) [1].

It is common amongst American children and is highly disseminated in American serials, talk shows and a documentary enacted by affected child artistes. Progeria was first described in an academic journal by Dr. Jonathan Hutchinson (1886) and Dr. Hastings Gilford4 (1897) in England. Thereafter, around 100 cases have been identified so far. It is a rare genetic condition because aging occurs in about one in eight million newborns and most of these affected children hardly survive before they step into adolescent stage. The maximum survival chances are not more than 30 years and the main cause for early death is cardiac failure. The average life expectancy of a child diagnosed with progeria is 13 years, but in some cases

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children died as early as 7 and some have survived till the age of 30.

HGPS is characterized by retarded growth, partial lipodystrophy, osteoporosis, osteolytic lesions, thin skin, micrognathia, and premature atherosclerosis. The affected children typically look normal at birth and in early infancy, but then grow more slowly than other children and do not gain weight at the expected rate (failure to thrive) [2].

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. 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.

A study from the Netherlands has shown an incidence of 1 in 4 million births. Currently, there are 80 known cases in the world. Approximately 140 cases have been reported in medical history.

Classical Hutchinson-Gilford Progeria Syndrome is usually caused by a sporadic mutation taking place during the early stages of embryo development. It is almost never passed on from affected parent to child, as affected children rarely live long enough to have children themselves (very few children with progeria even live past the teen years to be 21).

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.

In September 2011, the first reported case of a black African child with progeria was reported, 12-year-old South African Ontlametse Phalatse. The Progeria Research Foundation at Children's Hospital Boston, affiliated with the Harvard University Medical School, is treating her and monitoring her case [3,4].

CLINICAL MANIFESTATIONS

HGPS develops a characteristic facial appearance including prominent eyes, a thin nose with a beaked tip, thin lips, a small chin, and protruding ears. It also causes hair loss (alopecia), aged-looking skin, joint abnormalities, and a loss of fat under the skin (subcutaneous fat). This condition does not disrupt intellectual development or the development of motor skills such as sitting, standing, and walking. Over the course of the disease, the child's heart12 and circulatory abnormalities become progressively worse and are usually the most significant health problem for children with progeria. These children usually die from cardiovascular problems such as atherosclerosis, but some have died due to convulsions or various types of malnutrition.

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.

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. 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. 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 [6]. 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). 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. 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 [8].

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 rauten strauch syndrome, hallerman streiff syndrome and de barsy syndrome. Others, including mandibuloacral dysplasia or cockayne syndrome are diagnosed later in life, although they may have a neonatal onset.

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. 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 [9].

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 HGPS20 the measurement 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 a 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. Screening technologies could also be used to reverse nuclear membrane abnormalities in Progeria children's cells. 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 [10].

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 can be performed.

- Because HGPS has thus far not been reported to recur in families, prenatal testing would only be performed because of the (unlikely) possibility of germline mosaicism in one of the parents.
- 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)

It may be available for families in which the disease-causing mutation has been identified in an affected family member for laboratories offering PGD. Because HGPS has thus far not been reported to recur in families, PGD would only be performed because of the (unlikely) possibility of germline mosaicism in one of the parents [11].

HISTORY

Evidence of Hutchinson-Gilford progeria syndrome (HGPS) begins within the first 2 years of life. At birth, infants usually appear healthy, although sclerodermatous skin changes have been noted in some patients. Typically, the onset of the disease occurs at age 6-12 months, when skin changes and alopecia are first noted and when the infant fails to gain weight. The following are other suggestive findings:

- High-pitched voice Short stature and low weight for height, with prenatal onset of growth failure
- Incomplete sexual maturation Generalized osteoporosis and pathologic fractures
- Feeding difficulties
- Delayed dentition, anodontia, hypodontia, or crowding of teeth
- Low-frequency conductive hearing loss
- Hypertension
- Prolonged prothrombin time, elevated platelet counts, and elevated serum phosphorus levels
- Emotionally, patients with HGPS share the same feelings as age matched healthy persons with regard to expressing proper mood and affect.
- Intelligence is normal

Patients with HGPS are keenly aware of their different appearance and remain reserved in the company of strangers; in the presence of friends, they display affection and good social interaction.

Physical

The characteristic clinical findings of Hutchinson-Gilford progeria syndrome (HGPS) include abnormalities of the skin and hair in conjunction with characteristic facial features and skeletal abnormalities. The composite appearance of the characteristic facies and parieto-occipital alopecia create a "plucked-bird" appearance. Evidence of significant growth failure manifests within the first 1-2 years of life and prenatal growth failure is often apparent. Delayed, abnormal dentition is also common [12].

Causes

Hutchinson-Gilford progeria syndrome (HGPS) is related to aberrant processing of the nuclear envelope protein lamin A and accumulation of farnesylated prelamin A Autosomal dominant mutations in the *LMNA* gene, located on band 1q21.1- 1q21.3, are responsible for most cases of HGPS. De novo mutations associated with advanced paternal age are responsible for most cases, although maternal transmission of a mutant *LMNA* gene from an asymptomatic mother who manifested somatic and gonadal mosaicism has also been reported. In addition, autosomal recessive transmission has also been suggested to account for the reported development of HGPS in several sets of siblings born to unaffected parents.

The *LMNA* genes encodes the nuclear Atype lamins, which are type V intermediate Hair loss:

- Scalp hair and eyelashes are progressively lost, resulting in baldness with only a few vellus hairs remaining.
- Characteristic facies Protruding ears with absent lobes
- Beaked nose Thin lips with centrofacial cyanosis
- Prominent eyes
- Frontal and parietal bossing with pseudohydrocephaly
- Midface hypoplasia with micrognathia
- Large anterior fontanel
- Musculoskeletal abnormalities
- Thin limbs with prominent joints
- Joint contractures and coxa valga with mild flexion of the knees resulting in a wide gait and "horse-riding" stance
- Pyriform (pear-shaped) thorax with short, dystrophic clavicles

- Bilateral hip dislocations
- Other reported anomalies
- Dystrophic nails
- Hypertrophic scars
- Hypoplastic nipples

- Filament proteins that localize to the cell nucleus and form the nuclear lamina, a structure that supports the nuclear envelope. They are important in maintaining nuclear stability and organizing nuclear chromatin. The nuclear lamins may also play a role in regulating gene expression, DNA synthesis, and DNA repair [13].

- The most common *LMNA* mutation involves a C-->T transition at nucleotide 1824 (G608G). This substitution results in the activation of a cryptic splice donor site in exon 11, which results in a 150-base pair deletion and a truncated lamin A protein, called progerin.

- The abnormal progerin protein acts in a dominant-negative manner to prevent the normal assembly of nuclear lamins into the nuclear lamina. After translation, the mutant preprogerin protein undergoes normal farnesylation of a CAAX tetrapeptide motif located at the carboxyterminus.

- The farnesylated preprogerin protein is then incorporated into the nuclear membrane. However, the mutant, truncated protein lacks an important posttranslational processing signal required for cleavage of the preprogerin protein at the carboxyterminus. This cleavage is required for the release of prelamin A from the nuclear membrane, thus allowing its incorporation into the nuclear lamina. The abnormal progerin protein forms insoluble cytoplasmic aggregates [14].

- As a result of the absence of lamin A in the nuclear lamina, the cell nuclei from HGPS patients display abnormal nuclear blebbing and aberrant nuclear shapes. Abnormal chromosome segregation and delayed onset and progression of mitosis have also been demonstrated.

- The presence of the homozygous missense mutation G1626C (K542N) in *LMNA* was demonstrated in 5 siblings born to asymptomatic, consanguineous carrier parents. This study confirms that autosomal recessive inheritance of HGPS can also occur.

- A transgenic mouse model for HGPS has been created by introducing a splicing defect into intron 9 of the mouse *LMNA* gene. Transgenic mice display many of the features of HGPS, including loss of subcutaneous fat, decreased bone density, growth failure, craniofacial deformities, skeletal abnormalities, and early death.

- Using microarray analyses, 3 recent studies compared the gene expression profiles of cultured fibroblasts from patients with progeria with those of healthy people of various ages. In general, changes in gene activity detected in older patients correlated with changes in gene activity in progeria patients. Of the genes expressed differentially in progeria patients, several that help control mitosis were down-regulated. Many genes that control cell division and DNA or RNA synthesis and processing were also shown to be down-regulated in progeria patients; many of these changes are also seen with normal aging. Some of these changes were postulated to lead to genetic instability and a variety of disturbances in gene function.

- Changes were also seen in the expression of many genes involved in collagen remodeling and the formation of the extracellular matrix. In general, the changes favored excess extracellular matrix deposition, which may lead to the characteristic changes seen in the skin and the vasculature in progeria patients. Expression of transforming growth factor-beta, a factor that regulates tissue homeostasis and whose sustained expression is responsible for tissue fibrosis, is highly up-regulated in patients with progeria.

- The expression of several transcription factors, including many involved in musculoskeletal development, were also decreased in progeria patients. Expression of MEOX/GAX, a negative regulator of cell proliferation in mesodermal tissue, is elevated almost 30-fold in patients with HGPS, suggesting a contributory role in the development of the musculoskeletal abnormalities seen 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.

- Data from embryonic development suggest that changes in the level of hyaluronic acid are extremely important for morphological development. Experiments performed in chick embryos have demonstrated a correlation between cell differentiation and hyaluronic acid degradation. Hyaluronic acid is also necessary for the morphologic development of blood vessels in chick embryos. 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.

- In the past, studies of the link between progeria and aging (among other topics) have investigated the role of fibroblast life span.

- Cells from older donors exhibit a reduced number of cell divisions in comparison to younger donor cells. The reduction of life span in cultured fibroblasts derived from patients with progeria has revealed inconsistent results. A significant reduction in fibroblast life span has been claimed in some studies but has been questioned in later investigations. A recent thorough study indicates the life span of fibroblasts in culture is independent of donor age.

- Further abnormalities observed in cultured fibroblasts from patients with progeria include reduced mitotic activity, DNA synthesis, and cloning efficiency and a reduced capacity for DNA repair in cultured progeria fibroblasts after gamma irradiation. Mutant fibroblasts have been shown to demonstrate impaired DNA damage checkpoint signaling, which results in increased DNA double-strand breaks [15-18].

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.

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 [19].

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 [20]. 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 [21, 28-30].
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 [22]. 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 [23-25].

- 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 [26,27].

CONCLUSION

Progeria, eponymously named Hutchinson-Gilford syndrome, is a rare disease with less than 80 cases reported since the time of Hutchinson and Gilford at the turn of the century. 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.

REFERENCES

1. James William, Berger Timothy, Elston Dirk. Andrews' Diseases of the Skin: Clinical Dermatology (10th ed.). Saunders. 2005, p. 574.
2. Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P, Dutra A, Pak E, Durkin S, Csoka AB, Boehnke M, Glover TW, Collins FS. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature*, 423, 2003, 293–8.
3. Hutchinson J. Case of congenital absence of hair, with atrophic condition of the skin and its appendages, in a boy whose mother had been almost wholly bald from alopecia areata from the age of six. *Lancet*, 1, 1886, 923.
4. Gilford H. Ateleiosis and progeria: continuous youth and premature old age. *Brit. Med. J*, 2, 1904, 914–8.
5. Hennekam RC. Hutchinson-Gilford progeria syndrome: review of the phenotype. *Am. J. Med. Genet*., 140 (23), 2006, 2603–24.
6. Steve Sternberg (April 16, 2003). Gene found for rapid aging disease in children. USA Today. Retrieved 2006-12-13.
7. Korf B. Hutchinson-Gilford progeria syndrome, aging, and the nuclear lamina. *N. Engl. J. Med*., 358 (6), 2008, 552–5.
8. Grant, Matthew (22 February 2005). Family tormented by ageing disease. BBC News. Retrieved on 3 May 2009.
9. Hope, Alan (3 June 2009). Face of Flanders: Michiel Vandeweert. Flanders Today. Retrieved on 3 September 2009.
10. "Progeria: Treatment". MayoClinic.com. Retrieved 2008-03-17.
11. American Federation for Aging Research. (2004). Telomeres Information Center. http://www.infoaging.org/b-tel-5-role.html
12. Cook,A.(2002).Progeria. http://www.cmste.uncc.edu/Document%20Hold/ progeria.doc Accessed 2004, July 9.
13. Plasilova M, Chattopadhyay C, Pal P, Schaub NA, Buechner SA, Mueller H, Miny P, Ghosh A, Heinimann K. Homozygous missense mutation in the lamin A/C gene causes autosomal recessive Hutchinson-Gilford progeria syndrome. *J Med Genet*., 2004; 41, 2004, 609–14.
14. H, Hoeijmakers JH. Cell biology: ageing nucleus gets out of shape. Nature, 440 (7080), 2006, 32–4.
15. Scaffidi P, Misteli T. Lamin Adependent nuclear defects inhumanaging. *Science*, 312 (5776), 2006, 1059–63.

16. Haithcock E, Dayani Y, Neufeld E, et al. Age-related changes of nuclear architecture in Caenorhabditis elegans. *Proc. Natl. Acad. Sci*., U.S.A. 102 (46), 2005, 16690–5.
17. Liu B, et al. Genomic instability in laminopathybased premature ageing. *Nature Med*., 11, 2005, 780–785.
18. Brown WT, Zebrower M, Kieras FJ. Progeria: A genetic disease model of premature aging. In: Harrison DE (ed) Genetic Effects on Aging II. Telford Press, Caldwell NJ, 1990, pp 521-42.
19. Gordon LB, Harten IA, Calabro A, Sugumaran G, Csoka AB, Brown WT, Hascall V, Toole BP. Hyaluronan is not elevated in urine or serum in Hutchinson-Gilford progeria syndrome. *Hum Genet*., 113, 2003, 178–87.
20. James, William; Berger, Timothy; Elston, Dirk. Andrews' Diseases of the Skin: Clinical Dermatology. (10th ed.). Saunders, 2005.
21. Gray MD, Shen JC, Kamath-Loeb AS, Blank A, Sopher BL, Martin GM, Oshima J, Loeb LA. The Werner syndrome protein is a DNA helicase. *Nature genetics*, 17 (1), 1997, 100-3.
22. Wuyts W, Biervliet M, Reyniers E, D'Apice MR, Novelli G, Storm K. Somatic and gonadal mosaicism in Hutchinson-Gilford progeria. *Am J Med Genet A*, 135, 2005, 66–8.
23. Capell BC, Erdos MR, Masigan JP, Fiordalisis JJ, Varga R, Conneely KN, Gordon LB, Der CJ, Cox AD, Collins FS. Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson Gilford progeria syndrome. *Proc. Natl. Acad. Sci*., USA, 102(36), 2006, 12879-12884.
24. Arboleda G, Ramirez N, Arboleda H. The neonatal progeroid syndrome (Wiedemann- Rautenstrauch): a model for the study of human aging?. Exp Gerontol., 42, 2007, 939-943.
25. Gilkes JJ, Sharvill DE, Wells RS. The premature aging syndromes. *Br J Dermatol*., 91, 1974, 243- 62.
26. Gorlin R, Cohen M, Levin S. Hallermann- Streiff syndrome.In: Syndromes of the Head and Neck. (3rd ed.): New York: Oxford University Press 1990, pp. 306-308.
27. Paul R, Kapoor S, Puri R, Bijarnia S. Gerodermia Osteodysplastica. *Indian J Pediatr*., 71 (12), 2004, e77–79.
28. Gürakan F, Koçak N, Yüce A. Congenital generalized lipodystrophy: Berardinelli syndrome. Report of two siblings. Turk. J. Pediatr., 37 (3), 1995, 241–6.
29. Hernandez A, Aguirre-Negrete MG, Ramirez-Soltero S, Gonzalez-Mendoza A, Martinez-y-Martinez R, Velazquez-Cabrera A, Cantu JM. A distinct variant of the Ehlers- Danlos syndrome. *Clin. Genet*., 16, 1979, 335-339.
30. Chen L, Lee L, Kudlow BA, Dos Santos HG, Sletvold O, Shafeghati Y, Botha EG, Garg A, Hanson NB, Martin GM, Mian IS, Kennedy BK, Oshima J. LMNA mutations in atypical Werner's syndrome. *Lancet*, 362, 2003, 440–5.