Review Article

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Fortuitous Tale of Progeria & Oral Manifestations by Dentists

Dharti Gajjar[1*] Richa Wadhawan[2] Yehoshuva Reddy[3] Bhuvnesh Sharma[4] Dhaval Mehta[5] Mona J Shah[6]

[1]Senior Lecturer, Department of Oral Medicine and Radiology, Narsinhbhai Patel Dental College and Hospital, Visnagar, Gujarat, India.
[2]Senior Lecturer, Department of Oral Medicine and Radiology, Institute of Dental Education and Advance studies, Gwalior, MP, India.
[3]Professor and Head, Department of Oral Medicine and Radiology, Institute of Dental Education and Advance studies, Gwalior, MP, India.
[4]Senior Lecturer, Department of Oral Medicine and Radiology, Institute of Dental Education and Advance studies, Gwalior, MP, India.
[5]Professor and Head, Department of Oral Medicine and Radiology, Narsinhbhai Patel Dental College and Hospital, Visnagar, Gujarat, India.
[6]Reader, Department of Oral Medicine and Radiology, Facutly of Dental Science, Dharmsinh Desai University, Nadiad, Gujarat, India.

ABSTRACT

Background: Progeria is a rare, fatal genetic condition & an autosomal recessive disorder which comprises one in four million and one in eight million children of both sexes equally and described as premature and accelerated aging. The appearance and physiology of affected children be similar to elderly people but they typically have short life span. i.e. mid-teens. Hutchinson-Gilford syndrome & Progeria syndrome are synonyms, which was described by Johnathan Hutchinson in 1886 and further reported by Hastings Gilford in 1904. Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare genetic disorder in which the individual exhibits a phenotypic expression similar to that of an aged individual. Involved individuals suffer from numerous complaints generally seen in the elderly. HGPS individuals displayed many oral manifestations as well as a multitude of additional craniofacial manifestations of the disorder.

Keywords: Progeria, Hutchinson-Gilford syndrome, Genetic mutation, Growth failure.

INTRODUCTION

The word "Ageing" does not give a good perceptions to most of us due to complaints & diseases accompanying with ageing. Many individuals take large doses of vitamins & proteins etc., all in the optimism of discovering the "fountain of youth". According to social, behavioral, physiological, morphological, cellular and molecular changes, ageing can be reflected in numerous ways. Ageing stories, principally anti-ageing therapies having a huge attraction in newspapers and magazines. Although etiology of aging is vital to understand, but it is equally significant to distinguish the normal physiological changes from those associated with diseases. [1]. Aging can be described, according to Helfand and Rogina, as an inevitable consequence of being a multicellular organism; accompanying with a random, passive deterioration in function; indicating to a universal loss of homeostasis over time and mortality enhancing with age. [2]. Progeria is a uncommon, multisystem but devastating disorder involving various tissues and organs like bone, muscle, skin, subcutaneous tissue, vessels and heart that mimic premature aging. [3].

There are two types of progeria namely:

1) Hutchinson-Gilford Progeria Syndrome
2) Werner Syndrome (adult progeria)

1) Hutchinson-Gilford Progeria Syndrome

Progeria was first reported in 1886 by Jonathan Hutchinson. It was also explained independently in 1897 by Hasting Gilford. The

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*Correspondence Dr. Dharti Gajjar.
Department of Oral Medicine and Radiology, Narsinhbhai Patel Dental College and Hospital, Visnagar, Gujarat, India.
Email: Not Disclosed

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condition was later named Hutchinson-Gilford progeria syndrome.

Hutchinson Gilford Progeria Syndrome (HGPS; MIM 176670), is an extremely uncommon, sporadic genetic syndrome that revealed by premature aging of children with an estimated incidence of 1 per 4-8 millions live births. At April2012, the total number of known living children with HGPS was 89 worldwide according to data from the progeria Research Foundation [4].Busk (1972) studied the mode of presentation of 34 classical cases of progeria. Progeria is one of the numerous progeriod syndromes. The word progeria derives from Greek words "pro", meaning "before" or "premature", and "geras", meaning "old age". Progeria is a multisystem disorder involving various tissues and organs: bone, muscle, skin, subcutaneous tissue, vessels and heart [5].

2) Werner Syndrome (adult progeria)

Epidemiology of Werner syndrome includes one in one million individuals. Foremost sign of syndrome is around puberty when the child fails to have a normal growth spurt, or may be delayed until an individual is as old as 30 years. The characteristic features of this syndrome includes outstanding difference between person's appearance and his/her real age, greying hair and/or balding, wrinkling and aging of the face, sunken cheeks, small jaw, small stature (usually less than 1.6m tall), muscle weakness, thickened, tight and shiny skin over joints, leading to ulcers, high-pitched voice is seen. Occurrence of death in involved patients between 30-50 years most commonly due to heart disease or cancer [6].

Clinical features of Progeria includes:

Failure in normal growth of the body i.e. Growth failure during the 1st year of life, Loss of hair, aged look of skin, Joint stiffness, Dislocation of Hip, Generalized atherosclerosis, Cardiac diseases, Stroke, Thin, shrunken or wrinkled face, Baldness, Loss of eyebrows and eyelashes, Short stature, Large head for size of face (macrocephaly), Open soft spot (fontanelle), Small jaw (micrognathia), Dry, scaly, thin, wrinkled – aged looking skin, Restricted range of motion, Dwarfism, Small face and jaw in relation to size of head, Delayed tooth eruption or absence of tooth formation, Pinched nose, Mental growth of affected children is equivalent to other children of same age. Lifespan of affected children is limited to their early teenage years. Rarely they can survive up to the age of 21 or 22. In spite of being of dissimilar racial background, children suffering from the same disorder tend to have remarkably similar physical appearance & generalized atherosclerosis and cardiovascular problems [7].

Etiology of Hutchinson-Gilford Progeria Syndrome includes telomere dysfunction, altered gene protein interaction, epigenetic modification. Most serious feature of the same is cardiovascular disease because lifespan of HGPS is short, i.e. 11-13 years due to congestive cardiac failure, Myocardial infarction, cerebrovascular accident caused by progressive atherosclerotic disease [8].

Adult progeria is another well –known progeriod syndrome of adult onset condition also known as Werner syndrome. Etiology of the same includes mutation of the WRN gene which encodes a nuclear helicase. Patients of Werner syndromeexhibits limited life span i.e.normally up to the mid-teens & they fail to experience the usual pubertal growth spurt [9].

PATHOGENESIS

The nucleus is the significant feature of eukaryotic cells and is detached from the cytoplasm by the nuclear envelope (NE). The 3 different elements compose NE. They include nuclear membrane, nuclear pore complexes & the nuclear lamina. Nuclear lamina is a double unit membrane composed of outer nuclear membrane (ONM) & Inner nuclear membrane (INM). (ONM) is continuous with and shares biochemical and functional properties with the endoplasmic reticulum (ER). Whereas INM is different from ONM & ER, which is characterized by a subset of integral membrane proteins, termed nuclear envelope transmembrane proteins (NETs) that are anchored to the INM during interphase [10]Recently, awareness in the NE has intensified after the discovery of mutations in either protein of the nuclear membrane or lamins or nuclear pore complexes (NPC) proteins which may lead to a range of various inherited diseases, collectively termed nuclear envelopathies, If mutations arise in INM Or NPC proteins & if mutations arise in lamins

may give rise to laminopathies. NE proteins play important role in the functions of these proteins responsible for the normal development and/or maintenance of many different tissue types. So, NE proteins & its association with the wide range of diseases shows importance of these proteins in the growth, development & maintenance of different tissue types. Therefore many NE proteins have differential expression profiles throughout development and have been implicated in a range of cellular functions comprising the maintenance of cellular architecture, apoptosis, DNA replication, and transcription [10].Indeed, Mammals have three types of lamin genes, such as lamin B1 (LMNB1), lamin B2 (LMNB2) genes and the developmentally regulated lamin A/C gene (LMNA). B-type lamins produce the fundamental constituents of the nuclear envelope which are crucial for cell viability and normal embryonic development whereas A-type lamins possess more specified functions in terminally differentiated cells, fulfilling vital functions in organ and tissue homeostasis. They contain two major products lamin A and C which are expressed in virtually all differentiated somatic cells. [11]Although the A-type lamins are widely expressed, occurrence of different clinically defined disorders with tissue-selective abnormalities due to LMNA mutations [12]. Genetic studies since the late 1990s have demonstrated that mutations in LMNA may lead to a no. of clinical disorders with varied names. Broad classification includes diseases affecting primarily adipose tissue, striated muscle, peripheral nerve, or multiple tissues resulting in progeroid phenotypes [13]. Other researchers indicated that occurrence of progeria due to a single letter change in one gene of the child's DNA [14-16]. It is believed that mutation occurs in the father's sperm before conception that results in the production of a toxic protein that attaches to and distorts the nucleus (the cell's command center containing its genetic material). Although cells usually multiply during growth and development, the misshapen nucleus cannot divide appropriately, eventually damaging cells and accelerating the aging process [14]. It also has been revealed that patients with progeria have pronounced shortening of telomeres thus; telomere length may serve as a biologic clock regulating the life span of normal cells.It is assumed that telomeres become shorter with time because of a reduction in activity of the enzyme telomerase, which is responsible for the preservation of the normal telomeres length [15].A link between progeria and aging, was more intensified by the few other researchers among other topics & they assessed the role of fibroblast life span, immune function, endocrine function, lipofuscin accumulation, thermo-labile enzymes, atherosclerosis, and hyaluronic acid excretion [16]

ORAL MANIFESTATIONS

A) Jaws:

Micrognathia is the primary manifestation in progeria with relative paucity of vertical growth. Hypoplastic mandible with short ramus & obtuse mandibular angle may be present whereas in maxilla, smaller maxillary arch with presence of narrow palatal vaults & atrophic alveolar process & therefore overall craniofacial disproportion may be seen [17].

B) Teeth and its development:

Delayed tooth eruption with delayed loss of deciduous teeth and overcrowding may be associated with the same. Hence extraction of over retained primary teeth is advised [18,19]. Incidence of high caries, incomplete & abnormal formation of roots of primary molars, delay & irregular calcification of crowns of permanent teeth are seen. Some cases show Anodontia, Hypodontia & enamel hypoplasia. Position of lateral incisors may be seen lingually & palatally. Discoloration of teeth may be seen in some cases.

A) Other features:

There is narrow pulp chamber with calcification of nerve fibers & vessel wall may be noted [16]. Some cases reveal severe osteolysis with pathological fractures [20]

THERAPEUTIC APPROACH

To date, no effective therapy is existing for HGPS. HGPS remains incurable, with no therapy other than symptomatic treatment. However, not long after the discovery of a mutation in LMNA gene as the origin of HGPS, a number of potential therapeutic strategies have developed.

1. **PHYSICAL AND OCCUPATIONAL THERAPY** It can aid to retain physical activity and an active

lifestyle. It conservative management of Hip dislocation with physical therapy and body bracing and avoidance of surgical procedures on bones are suggested when possible.

2. **HYDROTHERAPY** It causes relief in pain, assistance in movement & relaxation & enables exercise.It can also help prevent arthritis from getting worse [21].

3. **NUTRINI** Infants with HGPS may show poor feeding. This delivers all of the nutrients essential for well-being and health [22]. Provision of sufficient nutritional intake may prerequisite placement of a gastrostomy tube for supplemental internal feeding.

4. **PRO-CAL** Pro-Cal is a new generation protein and calorie food enricher that can be added to a numerous food and drink to enrich the protein content of the normal diet with the least effect on taste, volume and texture [23].

5. **VITAMIN E** It is a fat soluble vitamin that guards vitamin A and essential fatty acids from oxidation in the body cells and inhibits breakdown of body tissues [24]. It is a antioxidant that protect the cells against the effect of free radicals can lead to cell damage that may contribute to the development of cardiovascular disease and cancer.

6. **EYE CARE** Corneal dryness and clouding should be fully assessed by an ophthalmologist. Usually, in HGPS this is exposure Keratitis and throughout daytime can be treated with moisturizing solution and during sleep with moisturizing ointment or by closing eyelids with skin tape [24].

7. **ASPIRIN** Based on the evidence from adult studies that low doses of aspirin help delay heart attacks and strokes, it is probably applicable to give children with HGPS low dose aspirin treatment, at doses of 2-3mg/Kg body weight per day. A small dose of aspirin is enough to inhibit dangerous blood clotting.This is beneficial to give people with narrowed coronary arteries which is common place in children with progeria [26].

8. **FLUORIDE**

All progeria children have problems with their teeth. Under development of the facial bones and the lower jaws leads to late eruption of the teeth, they can be small, irregularly formed or even missing and tooth decay is common. Fluoride can greatly beneficial for dental health by strengthening the tooth enamel, making it more resistant to tooth decay [26].

9. **GROWTH HORMONE**

Growth hormone has been attempted [27]. The use of Morpholinos has also been attempted in order to decrease progerin production. Antisense Morpholino oligonucleotides specifically directed against the mutated exon11-exon12 junction in the mutated pre-mRNA were used [28].

ANTI-CANCER DRUGS

RapamycineRapamycine also called Sirolimus is a macrolide. There are recent studies concerning Rapamycine which conclude that it can decrease the phenotypic effects of progeria fibroblasts and abolishment of nuclear blebbing, degradation of progeria in affected cells and lessening of insoluble progerin aggregates formation [29].

Statin Pravastatin: Pravastatin traded as Pravachol or Selektine. It is normally used for the reduction in cholesterol and preventing cardiovascular disease [30]

Bisphosphonate

Zoledronic Acid: It is also called Zometa and Reclast. It is usually used for improving Osteoporosis and to inhibit skeletal fractures [30]

Farnesyltransferase inhibitor An experimental treatment with Farnesyltransferase inhibitors (FTIS) started in Boston, and European children were given a different therapy with a combination of statins and amino-Bisphosphonate in Marseille. The last combination of medication is also now used in Boston [31].

DIAGNOSIS

There is no biochemical test for diagnosing progeria. These patients may excrete greater amounts of hyaluronic acid, but the underlying

molecular defect is unknown. It is uncertain whether abnormal findings such as insulin resistance or an increased basal metabolic rate (BMR) occur in all individuals with progeria [20]. However the diagnosis of HGPS is usually straightforward, and the classically affected patients strongly resemble one another. Although there is a group of patients with progeria that show a definite overlap with patients with mandibulo-acraldysostosis (MAD). Their clinical findings vary from classical HGPS in numerous respects:

a) Growth is less underdeveloped, adult heights ranging from 130 to 145 cm, while in classical HGPS height rarely exceeds 115cm; b) In many, scalp hair perseveres much longer, and may not vanish completely even in old age; c) The lipodystrophy progresses more slowly with fat pads remaining in the cheeks, submandibular region, and pubis into adulthood; d) Osteolysis is more severe in all involved bones (vault, mandible, clavicles, ribs, distal phalanges) except for the viscera-cranium where it is mild in childhood and only gradually progresses later on. The more severe osteolysis rises the risk of fractures, especially of the humerus, often at a young age (in 10 of the families, affected children had fractures, usually from the age of two to three years); e) The incidence of consanguinity is raised (four in fourteen families); f) The chance of survival into adulthood is somewhat higher (four cases having reached an age of 20 years or above) [32].

FUTURE ASPECT

The children with progeria undergo coronary artery bypass surgery and/or angioplasty in attempts to ease the life-threatening cardiovascular complications resulted by progressive atherosclerosis [5].However, there currently is no treatment or cure for the underlying condition. Death occurs on average at age 13; usually from heart attack or stroke [32].Researchers published cell culture and mouse model studies that support a potential drug treatment for children with Progeria. Farnesyltransferase inhibitors (FTIs), originally developed for cancer, are capable of reversing the dramatic cell structure abnormalities that are the hallmark of cells from children with Progeria. Studies on progeria also inspected the damage the mutant protein does to blood vessel cells of humans and mice [32]. The discoveries propose increased hope for a cure for progeria and may also offer key insight into the source of adult heart disease.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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