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An Overview of Hutchinson Gilford Progeria Syndrome (HGPS)

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MT and ML designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors MT, CF, ET and ML managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Hutchinson Gilford Progeria Syndrome (HGPS) is a rare genetic disorder. The disorder is characterized by premature aging, generally leading to death. The purpose of this article is to review Hutchinson Gilford Progeria Syndrome and its characteristics. There are many symptoms from various organs such dermatology characteristics, facial features, and musculoskeletal disorders. The syndrome is characterized by specific radiological and histological findings. The diagnosis is based on the identification of common clinical features and the detection of mutation of specific gene. There are some types of treatment may facilitate or delay some of the signs and symptoms.A multidisciplinary team should intervene in order to increase the quality of life and survival of Hutchinson-Gilford progeria syndrome.

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1. INTRODUCTION

Hutchinson Gilford Progeria Syndrome [1,2] (HGPS) or Progeria Syndrome [2] is an extremely rare hereditary disease which affects skin, musculoskeletal system and blood vessels and is characterized by manifestations of premature aging [3,4]. The reported incidence of HGPS is 1 in 8 million new births, although the true figure may be closer to 1 in 4 million [5]. Mainly it is observed in Caucasians (97%) [6].

Progeria is associated with severe morbidity and mortality as a result of accelerated atherosclerosis of cerebral and coronary arteries, leading to premature death during the first or second decade of life. Patients presenting with HGPS and other symprtoms which accelerate aging, such as poor growth, atrophy of muscle and skin, loss of subcutaneous fat, osteoporosis, arthritis, alopecia and occasionally tumors, cataracts, diabetes, and hyperlipidemia [3,7,8]. Also, kidneys, brain, adrenals, liver, testis and heart can be infected [9].

The disease was first described by Dr Jonathan Hutcinson and later Dr Hutchinson Gilford expanded on previous observations. The word progeria is derived from ancient Greek origins ("pro" from the Greek word for "before" or "forward" and "geron" meaning "old person") [10].

A literature review was conducting using the electronic databases PubMed and Google scholar from the years 2000-2014. There were used the following key words: "Hutchinson Gilford Progeria Syndrome", "treatment'', "symptoms" and the combination of them. Exclusion criteria of articles were the language, except English and Greek.

2. PURPOSE

The purpose of this article was to review Hutchinson Gilford Progeria Syndrome and its characteristics.

3. ETIOLOGY

In 2003, researchers at National Human Genome Research Institute (NHGRI) together with the Progeria Research Foundation, the Institute of Basic Research for developmental disabilities in New York (New York State Institute for Basic Research) and the University of Michigan discovered that Hutchinson-Gilford progeria is caused by a tiny, point mutation in a single gene, known as lamin A (*LMNA*) [11]. Lamin A (LMNA) is a protein that contains a layer that is attached to the inner nuclear membrane, which consists of a family of polypeptides with the major component being the lamin A, B1, B2 and C. Lamins A and C are formed by alternative splicing (online) copy of the gene LMNA [12]. The researchers found that the mutation responsible for the HGPS causes LMNA gene produces an abnormal form of the protein lamin A, which destabilizes the nuclear membrane of the cell in a way that can be particularly damaging to tissues that normally subject to intense physical power, as cardiovascular and musculoskeletal system [13]. It has been observed increased levels of hyaluronic acid, which is responsible for sclerodermatous. The most common mutation is a HGPS G608G (GGC> GGT) mutation in exon 11, which functions as a dominant negative change in the characteristics of the genus [5,14].

The HGPS diagnosis is based on the detection of either c.1824C > T (p.Gly608Gly) heterozygous mutation in the LMNA classical HGPS form or one of the three heterozygous mutations LMNA c.1822 G > A (p.Gly608Ser), c.1821 G> A (p.Val607Val), or c.1968 +1 G > A in atypical HGPS. The LMNA gene is known to be associated with HGPS. More simply, it is based on finding G608G mutation in exon 11 of the gene LMNA, which is presented in all patients with HGPS [15].

The disease usually transmitted in accordance with an autosomal dominant inheritance pattern [8]. It has also been reported in brothers, which passed with an autosomal recessive inheritance pattern [16]. According to Nordqvist (2012) "A non-twin child runs the same risk of suffering from progeria, like any other child from another family. One in every 100 cases of HGPS, the syndrome has been passed to the next generation within the same family." [17] Also, Pollex and Hegele reported that "there are many cases of progeria were observed in families in which the parents were not related, suggesting sporadic autosomal dominant inheritance which has been confirmed with the discovery of the causative mutations" [5].

4. COMMON SYMPTOMS AND COMPLICATIONS

Clinical investigations revealed that there are many clinical manifestations. The dermatology characteristics include: loss of eyebrows and eyelashes [18,19], generalized alopecia [19], nail dystrophy, sclerodermatous in the lower abdomen and proximal thighs with irregular bumps because of underlying lipodystrophy [18,19]. Also, there are prominent scalp veins [19,20], hyperplastic scars and relaxation and wrinkling of the skin due to loss of subcutaneous fat, especially in the hands and feet with café au lait spots in various regions of the body [9]. The facial features includes crooked nose, extraocular, lagophthalmus [9], thin lips with central-face cyanosis [18], disproportionately large head with the face [9], midfacial hypoplasia with micrognathia [19] and overriding ear flaps / absence of lobes [21].

The musculoskeletal disorders are bilateral dislocation of hip, pear-shaped thorax with short, dystrophic clavicles their weight is significantly less than their height [22], swollen synovial joints, thin membership with projection of the joints, distal phalangeal osteolysis and contracture of the joints [9,20]. Furthermore, there are some other clinical points, such as delayed and crowded teeth, thin and shrill voice, cataract lens, tumors, insulin resistance and hypoplasia of the nipples of the breasts [9,21]. These characteristics are presented in Table 1.

According to Parreno & Cruzz (2011) the following symptoms are appeared during the first years of life: The first signs of HGPS are circumoral cyanosis and a visible vein across the nasal bridge. Children present in their first to third of year of life, skin complications, hair loss and joint deformities. Within the first year, growth is disturbed and pitting edema is seen in the lower abdomen, upper gluteal area, genitalia, and anterior thighs. Pitting edema can arise anywhere from one and a half months to two years. Alopecia usually takes place within six months to two years. Lipodystrophy is observed in early as six months and osteolysis of the acromial ends of the clavicles and upper ribs eventually results in characteristic narrow shoulders and pear-shaped thorax. Decreased joint mobility is appeared around age two or three years [10]. The above symptoms are presented in Table 2.

A severe complication of progeria is advanced atherosclerosis, which is usually manifested without apparent abnormalities in lipid profiles [23]. Atherosclerosis leads to severe cardiovascular complications during childhood and adolescence or early adulthood, such as myocardial infarction, congestive heart failure, interstitial fibrosis, diffuse myocardial fibrosis and calcification of the aorta and mitral [24,25]. The cerebrovascular complications are the result of cerebrovascular infarcts which are hemiplegia, subdural hematoma and seizures.

Table 1. Characteristics of HGPS

Dermatology characteristics	• Loss of eyebrows and eyelashes generalized alopecia • Nail dystrophy • Sclerodermatous in the lower abdomen proximal thighs with irregular bumps because of underlying lipodystrophy prominent scalp veins • Hyperplastic scars and relaxation and wrinkling of the skin especially in the hands and feet with café au lait spots in various regions of the body.
Facial characteristics	• Crooked nose • Extraocular • Lagophthalmus thin lips with central-face cyanosis • Disproportionately large head with the face • Midfacial hypoplasia with micrognathia overriding ear flaps/ absence of lobes.
Musculoskeletal disorders	• Bilateral dislocation of hip • Pear- shaped thorax with short, dystrophic clavicles • Weight is significantly less than their height • Swollen synovial joints • Thin membership with projection of the joints • Distal phalangeal osteolysis and contracture of the joints.

Table 2. Clinical signs of HGPS and time of presentation

Age	Symptoms
1,5 months	Sclerodematous skin
2 months	Circumoral sclerodematous skin, visible scalp vein
< 1 year	Failure to thrive, growth deficiency
6 month -2 years	Alopecia
6 month	Lipodystrophy
2-3 years	Decreased joint mobility, contractures, osteoarthritis
>7 years	Cardio and cerebrovascular manifestations

Other causes of morbidity and mortality include wilting, strokes, loss of mobility, fatigue and accidental head injury [6,19]. Mortality is a result of heart and cerebrovascular disease (heart attack or stroke) and appears generally at the age of 6-20. The average life span of these patients is about 13 years, although some patients surviving to the age of 45 [26].

5. RADIOLOGICAL AND HISTOLOGICAL FINDINGS

The radiological findings are usually observed in the first or second year of patient's life, especially in the skull, thorax, long bones and phalanges. These findings are the followings: diffuse osteopenia, acro-osteolysis of phalanges, peripheral keys, senior sides and proximal humerus, vertebral bodies like "fish mouth", valgus hips, thinning of the skull diplois, thinning of the long bones and widening of metaphyses, vormiana ossicles, open cranial sutures and sources, marrow hypoplasia and facial sinuses, hypoplasia of the jaw, subtle and sloping sides and, lastly, small chest cage [19,27].

Furthermore there are radiological features such as: Thin calvarium and relatively large, the diploic space is absent or very shallow; the face is small with a disproportionate small mandible. The ascending rami of the mandible are very short. Vascular markings and wormian bones are conspicuous in the large thin calvaria. The clavicles are small in caliber and rarefied at birth; the ribs are abnormally gracile and the posterior segments of the upper four ribs on both sides may also disappear in early childhood. The long bones are shortened and the greater trochanters are bizarre in shape and position [28].

The histological examination of skin lesions characteristic shows scleroderma. In the early stages, the epidermis shows moderate acanthosis and small reduction skinfold. The dermis may contain thick collagen bundles. Progressively, homogenized collagen is deposited, which is extended into the subcutaneous tissue. Additionally, in the upper layer of the dermis can be observed mild perivascular infiltration and the amount of acidic polysaccharides increases [19]. In the later stages, the subcutaneous fat is significantly reduced, except from some scattered fat lobules surrounded by connective tissue. The blood vessels are moderately thickening the muscular wall and narrowing the vascular lumen. The hair follicles might be atrophic [19].

6. DIAGNOSIS

The diagnosis is usually made by age 2 [18]. The diagnosis is based on the identification of common clinical features and in aforementioned mutation of LMNA.

The differential diagnosis contains acrogeria (type of Gottron) [29], eosinophilic fasciitis, youthful scleredema (sclerema neonatorum), neonatal progeroid syndrome (Weidemann-Rautenstrauch syndrome) [30], familial mandibuloacral dysplasia, gerodermia osteodysplastica, restrictive dermopathy, progeroid Petty-Laxova-Weidemann syndrome, congenital personal dystrophy, systemic sclerosis, Rothmund-Thomson syndrome, Cockayne syndrome, pangeria (Werner Syndrome), Seckel syndrome, stiff skin syndrome, Hallermann-Streif syndrome, progeroid type of Ehlers-Danlos syndrome, DeBarsy syndrome, Berardinelli-Seip syndrome, Donahue Syndrome and GAPO syndrome (growth retardation, alopecia, pseudo-anodontia, optic atrophy) [22].

The onset of Werner syndrome might occur in individuals in their mid-teens or it may be delayed until an individual is as old as 30 years. Death usually occurs when patients are aged 30-50 years because of atherosclerosis or malignant tumors. Rothmund-Thomson syndrome is characterized by short stature, cataracts, pigmentation of skin, baldness, abnormalities of bones, nails and teeth. Cockayne syndrome

spans a spectrum that includes CS Type 1, CS Type 2, a more severe form with symptoms present at birth, CS Type 3, a milder form; and xeroderma pigmentosa-Cockayne syndrome (XP-CS). The features of Type 1 and Type 2 are: growth deficiency, premature aging and pigmentary retinal degeneration along with a complement of other clinical findings [28].

7. TREATMENT

There is no cure for premature aging [19,31]. However, a regular monitoring of cardiovascular disease can help managing the situation. Some children undergo bypass surgery or coronary artery dilation of cardiac arteries (angioplasty), in order to slow the progression of cardiovascular disease. Also, some types of treatment may facilitate or delay some of the signs and symptoms.

These include:

- Treatment with farnesyltransferase inhibitors (FTIs) to prevent prelamin A anchoring to the nuclear membrane [10].
- A daily low - dose aspirin can help to prevent heart attacks and strokes [19,31].
- Depending on the child's condition, the doctor may prescribe other medications such as statins, which lower cholesterol or blood thinners with the aim of preventing blood clots. The use of growth hormone can help the increase of height and weight [31].
- The use of statins and bisphosphonates result in reduced lipodystrophy, reduce hair loss, improve bone defects, and enhance longevity [10].
- Physical and occupational therapy: These can help joint stiffness and hip problems and allow the child to remain active [19,31].

Furthermore, there is an investigation treatment in progress. Such a treatment contains drugs, known as inhibitors of farnesyltransferase inhibitors (FTIs), which was developed aiming cancer cure, has promised to correct the defective cells that cause premature aging, in laboratory studies [32,33].

8. CONCLUSION

A multidisciplinary team should intervene in order to increase the quality of life and survival of Hutchinson-Gilford progeria syndrome. The syndrome is rare and there are new therapeutic approaches in order to alleviate the symptoms. There is a great need for further research to manage the symptoms of this disease.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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