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Case Report
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Case Report of an Iraqi Patient with Progeria and Pulmonary Fibrosis

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Abstract

Hutchinson-Gilford progeria syndrome is a rare genetic disorder. It was reported in literature as one case in eight million and causes growth retardation, hair loss, lipodystrophy, scleroderma-like skin and pulmonary changes, osteolysis, early atherosclerosis and facial features that resemble those of older people. Here, we report the case of a 16-year-old Iraqi girl with Hutchinson-Gilford progeria syndrome and pulmonary Fibrosis.

Introduction

Progeria is a rare disorder of early aging characterized by thin skin, skeletal abnormalities, with systemic especially cardiovascular manifestations.

The classic form is known as Hutchinson-Gilford syndrome, of a sporadic occurrence with an incidence of one in eight million births, male to female ratio of 1.5:1 [1].

In this syndrome, aging process is accelerated up to seven times that of normal. The average life span is about 13 years (ranging from 7 years to 27 years) with unusual survival till the age of 45 years. Death is mainly due to cardiovascular complications like myocardial infarction or congestive heart failure [2]. People from all ethnic backgrounds can have progeria, and all share similar appearance [3].

The probable cause is thought to be a genetic mutation in the lamin gene located in the nuclear matrix which causes an aberrant form of the inner nuclear membrane protein lamin A, called progerin to accumulate resulting in cellular dysfunction.

A study found that mutant lamin A can decrease the telomere length via a direct effect. One of the most important genetic links between progeria and aging is telomere ends shortening with each replication cycle [4,5].

Child's failure to thrive is attributable to the inactivity of growth hormone and lack of vascularization caused by excessive production of hyaluronic acid which leads to the sclerodermatous changes and cardiovascular problems. Treatment is usually directed towards the main complaints with hopes for the success of the ongoing clinical trials studying a possible Break through therapy for the devastating condition.

The value of coronary artery bypass surgery or percutaneous transluminal angioplasty has been reported in some cases with cardiovascular events. Low doses of aspirin could be used in the prevention of cardiac attacks or cerebrovascular events. Anesthetic drugs should be used with caution. Special nutritional therapy was proposed in a study and slightly improved weight gain and growth. Combined nutritional therapy and GH treatment improved growth, levels of growth factors and decreased the basal metabolism rate. Extractions of delayed primary teeth may be required to avoid crowding or development of double rows of teeth [6]. A new promising treatment for the disorder with the Farnesyl Transferase Inhibitors (FTI) called Lonafarnib, results from this clinical treatment trial for children with HGPS provide preliminary evidence that lonafarnib may improve weight gain, vascular stiffness, bone growth, and hearing. Other therapies currently under research include Pravastatin and zolindronic Acid [7].

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Figure 1-3: The girl had a skin and bone appearance, protruding ears, long easily pluckable hair, abnormal gait, thin atrophic stretchable skin, loss of subcutaneous fat around the extremities, mild kyphotic spine, shortened blunted and drum-like digits with preserved nail bed angles, pectus carinatum.

Case Presentation

A 16 year old girl was referred to the rheumatology consultant clinic at Baghdad teaching hospital from the chest clinic for evaluation and treatment as a case of juvenile systemic sclerosis with interstitial lung disease, upon seeing the patient, who indeed was suffering from progressive exertional shortness of breath, it was well noticed that she had scleroderma facies with other features including loss of eyelashes and eyebrows, sunken eyes, small chin, protruding teeth and a striking loss of fat all over the body, she had short blunted fingers and toes, kyphotic spine and protruded chest, her skin was thin and pinch-able, and she had prominent forehead veins. These findings alerted us to the possibility that we were dealing with a case of progeria rather than systemic sclerosis.

The patient gave history of indigestion with heartburn, poor appetite, constipation, progressive loss of hair, and headaches, she did not have history of joint pain, muscle weakness, skin changes, or Raynaud's phenomenon.

She had her first cycle at the age of 14, and been regular ever since. The teenage was a product of normal vaginal delivery with an uneventful intrauterine life, she was well at birth but the parents noticed exceptionally worrisome small lips that they have seen before with a similar family member (the patient's cousin) who died at the age of 20.

Her parents share third degree consanguinity, and have 4 children two of them are normal with another 9 year old with the same morphological appearance as our case. During the past few years, the parents sought medical advice to treat their child, and never reached a diagnosis, the closer opinion was the possibility of systemic sclerosis, based on which the patient underwent barium swallow to asses for esophageal dysmotility.

The school performance of the patient was normal till the deformed little fingers were no longer capable of holding the small thin pencil correctly, which along with bullying from peers lead to the joined family and teachers decision to stop schooling at the 2nd primary class.

The girl had a skin and bone appearance, protruding ears, long easily pluckable hair, abnormal gait, thin atrophic stretchable skin, loss of subcutaneous fat around the extremities, mild kyphotic spine, shortened blunted and drum-like digits with preserved nail bed angles, pectus carinatum (Figures 1-3). The patient had mild frontal bossing, a beaked nose, protruding eyes, a high pitched voice, and

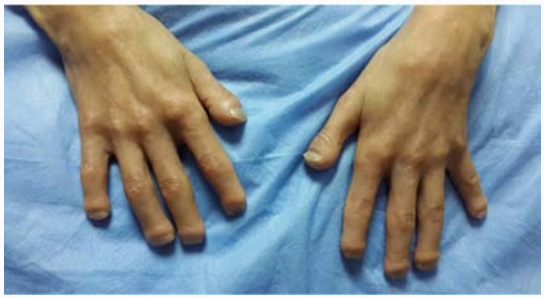

Figure 4: Opening of mouth was restricted (interincisal distance 21 mm) and the teeth appeared large, protruded and eroded.

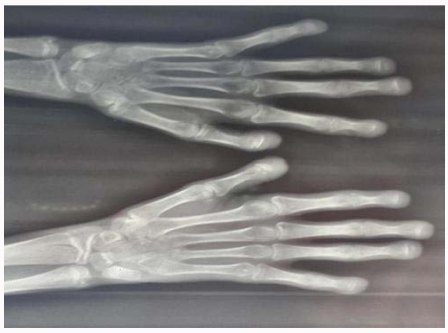

Figure 5: X-rays of the Patient's hands showing Osteopenia with Acro-Osteolysis, X-ray of the pelvis showing Coxa Valga.

hypoplastic maxilla and mandible with mild mid facial deformity giving "plucked bird appearance." Opening of mouth was restricted (interincisal distance 21 mm) and the teeth appeared large, protruded and eroded (Figure 4).

She had fair air entry with fine inspiratory crepitations in the middle and lower chest zones. Based on history and clinical findings, a provisional diagnosis of progeria was made. To confirm the diagnosis, the child was subjected to radiological and biochemical investigations. Biochemical investigations were normal apart from elevated serum cholesterol of 200 mg/dl. The Complete blood picture and ESR were normal.

Her serology for Rheumatoid factor Anti citrullinated peptide antibody and antibodies to extractable nuclear antigens were negative. Radiographic studies of the hands revealed acroosteolysis of the terminal tufts of distal phalangies with decreased bone density, reduced joint space of the carpometacarpal joints and intercarpal

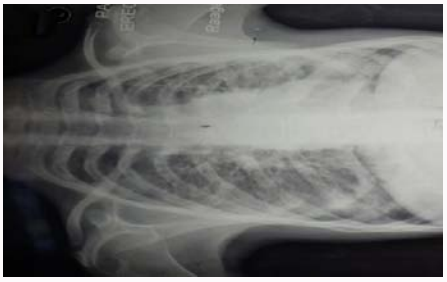

Figure 6: CXR of the patient showing osteopenia of the distal Clavicles.

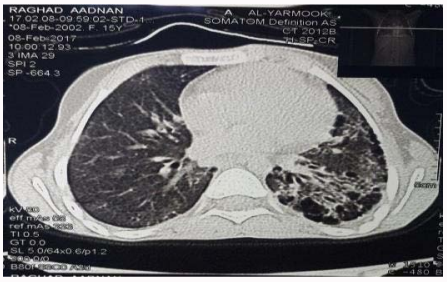

Figure 7: HRCT of the patient showing Ground Glass opacities with honeycombing and traction Bronchiactasis.

joints (Figures 5,6).

High resolution computed tomography of the chest showed diffused ground glass appearance with peripheral honey combing and traction bronchiectasis with dilated lower oesophagus (Figure 7).

Her barium swallow and meal showed lower oesophageal dilatation with delayed emptying, normal brain CT scans,

DEXA scan of the spines' Z score was at -1.8. The patient was put on Domperidone and Statin therapy.

Discussion

Progeria is a rare genetic disorder of early aging characterized by thin skin, skeletal deformities, with systemic complications. In The classic form -Hutchinson-Gilford- syndrome, aging process is thought to be accelerated up to seven times that of normal. The average life span is 13 years (ranging from 7-27 years) with unusual survival till the age of 45 years, our patient is still at the age of 16 but her similar cousin died at the age of twenty. The affected children are normal at birth and may grow at normal rates till the end of the first year, when weight gain and growth rates slow down, this was the same pattern described by her mother.

Progeria does not impact the child's neurological development, motor skills, or intelligence, and it does not cause higher risk of infection so children with the condition can sit, stand, and walk like any other child and the patient indeed had normal milestones [8].

Loss of hairs and subcutaneous fat along with sclerodermatous changes give rise to a "plucked bird" appearance as seen in the pictures. accompanied by stiffness in the joints, visible veins, narrow, wrinkled, or shrunken face, a head that is larger compared with the body, a small jaw bone, slow tooth development (Figures 1-4), a high-pitched voice, limited range of motion and possible hip dislocation, piriform chest, short clavicles, horse riding wide based gait due to coxa valga, distal bony osteolysis, accelerated atherosclerosis, leading to cardiovascular disease and stroke [9].

Increase in blood and serum levels of low-density lipoprotein and cholesterol and total lipids is commonly seen which was the case in this patient [4,5]. Other anomalies frequently present in Hutchinson-Gilford progeria are and spots of brown skin lesions, hypotrichosis, absence of eyelashes and eyebrows, delayed closures of fontanels and sutures, beaked nose, perioral cyanosis, Thin lips, protruding ears with absent lobes, and dystrophic nails with Short terminal phalanges.

Individuals with progeria syndromes are also at higher risk of fibrotic disorders like pulmonary and myocardial fibrosis [7,8]. Although not classically documented, pulmonary fibrosis was found in this young girl and her deceased relative [10-12].

This association is partly explained by the studies showing that Idiopathic Pulmonary Fibrosis (IPF) is increasingly being recognized as the most common manifestation of telomere-mediated disorders and telomerase mutations also are the most frequent cause of familial IPF [13]. This explains the association of progeria with pulmonary fibrosis and oesophageal dysmotility in the current case.

Although absence of complete sexual maturation has been considered characteristic of the syndrome, some may not follow this rule and may even reproduce which means that the presence and regularity of the menstrual cycle of this lady do not exclude the diagnosis of progeria [14].

Many other premature aging syndromes, which are called progeroid syndromes, need to be distinguished from progeria. Neonatal progeroid syndromes are evident at birth and include Wiedemann Rautenstrauch syndrome. Hallerman-StreiL syndrome and De Barsy syndrome. Others like Mandibuloacral dysplasia or Cockayne syndrome are diagnosed later in life, although they may present in the early neonatal period. Werner syndrome and acrogeria, stiff skin syndrome, Restrictive Dermopathy and pseudoscleroderma syndromes can be also mistaken with HGPS [15,16].

All these syndromes have characteristic physical findings that made the HGPS more likely in this case, like the absence of ocular abnormalities and the fat depositions and the pinchable skin.

Diagnosis currently depends upon recognition of clinical and radiographic findings which are typical in this patient. The finding of the common LMNA truncating mutation can also be helpful in the diagnosis; unfortunately the genetic study is not available in Iraq.

The characteristic radiological abnormalities are found in the skull, thoracic cage, Long bones and phalangies. In the skull, hypoplastic bones with patent fontanelles and sutures. In the long the long bones, Thinning and resorption of the distal clavicles which is described as the most consistent abnormality found in chest X-ray followed by Narrowing of the posterior ribs. Other long bones are slender with thin cortices. Coxa valga is a consistent finding and sometimes coxa vara is seen [17]. The progressive bone loss from the distal phalanxes of the fingers and/or toes is one of the hallmarks of the disease [18].

All of these anomalies were present in this case. No effective therapy is currently available to cure the disease. However, symptomatic treatment should be proposed for its complication, including orthopedic complications.

The main complication of progeria is coronary artery disease, and monitoring for cardiovascular disease should be obtained at least annually. Thus this girl was started on statin therapy and was

registered in hopes for getting the right genetic study and potential participation in a clinical trial.

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