Case Report:

Hutchinson-Gilford Progeria Syndrome.

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Abstract: Hutchinson-Gilford Progeria syndrome (HGPS) is a rare pediatric genetic syndrome associated with a characteristic aged appearance very early in life, generally leading to death in the second decade of life. Apart from premature aging, the other notable characteristics of children with HGPS include extreme short stature, prominent superficial veins, poor weight gain, alopecia, as well as various skeletal and cardiovascular pathologies associated with advanced age. The pattern of inheritance of HGPS is uncertain, though both autosomal dominant and autosomal recessive modes have been described. Recent genetic studies have demonstrated mutations in the LMNA gene in children with HGPS. In this article, we report a 16 years old girl who had the phenotypic features of HGPS and was later confirmed to have LMNA mutation by genetic analysis.

Key Words: Alopecia, Hutchinson-Gilford Progeria Syndrome, Poor weight gain, Premature aging, Short stature.

Introduction:
Hutchinson-Gilford Progeria syndrome (HGPS) is a rare and uniformly fatal segmental "premature aging" disease that affects a variety of organ systems. (1) Aging in an inevitable process of bodily changes that eventually results in decreased physiological capacity, decreased ability to maintain homeostasis, and increased vulnerability to disease processes. However, in children with HGPS these changes occur rapidly, usually during the first decade of life. (2) HGPS has a reported incidence of approximately 1 in 8 million live births and about 144 cases have been described in literature worldwide. (3, 4) Though the clinical presentation is typical, conventional radiological and biochemical investigations help in confirming the diagnosis. Herein, we describe a 16 years old girl who presented to us for evaluation of chronic cough, delayed puberty and poor weight gain, but incidentally had the physical and radiological changes described in association with HGPS.

Case Report:
A 16 years old girl, 4th born to non-consanguineously married couple was referred to our institution for evaluation of chronic cough and poor weight gain. She was delivered at term in a hospital with an uneventful antenatal and post-natal history. Mother had noticed that her daughter was not gaining adequate weight and height since early childhood and also that her permanent teeth had not erupted completely following the fall of her temporary teeth. She had multiple OPD visits for the same and was prescribed multivitamins and hematins and reassured. She had also developed tuberculosis, with proportionate short stature and delayed puberty secondary to an endocrine disorder was considered and evaluated.
She had normocytic normochromic anemia (Hemoglobin – 8.5g/dl) with elevated ESR (70mm first hour) and lymphocytic leukocytosis. Mantoux test was strongly positive. Pneumonic infiltrates were seen in bilateral lung fields. Her skeletal survey revealed generalized osteopenia. She had a large cranium with widened sutures (especially lambdoid suture) and multiple wormian bones. Maxilla and mandible were hypoplastic (Fig 4). There was osteolysis and resorption of the terminal phalanges (acroosteolysis) of both hands and feet (Fig 5). Ophthalmological evaluation revealed decreased visual acuity due to bilateral early cataractous changes. Her bone age, hearing and endocrinological evaluation including the levels of thyroid hormones, parathormone, growth hormone, adrenal hormones and insulin were normal. Ultrasound abdomen and neuroimaging did not reveal any abnormality. Genetic analysis revealed a 46XX karyotype with homoygous mutation involving the LMNA gene. Based on the phenotypic features, radiological findings and genetic analysis a final diagnosis of Hutchinson-Gilford progeria syndrome with pulmonary tuberculosis was made. Parents were counseled regarding her condition and the prognosis associated with it. Meanwhile, she was started on anti tuberculosis therapy following which her cough decreased significantly and her appetite improved. Subsequently she was lost for follow-up.

Figure 1: Showing (i) depressed nasal bridge and prominent nose (ii) malar flattening (iii) melanin pigmentation of tongue (iv) partial anodontia.

Figure 2: Showing (i) Short stubby fingers and toes with dysplastic nails.

Figure 3: Showing scoliosis and genu valgum.

Discussion
First described in 1886 by Dr. Jonathan Hutchinson, Dr. Hastings Gilford subsequently expanded on Hutchinson’s observations and derived the word “progeria” from ancient Greek origins (“pro” from the Greek word for “before” or “forward” and “geron” meaning “old person”) to describe this accelerated segmental premature aging syndrome. De Busk in 1972 renamed this condition as Hutchinson-Gilford progeria syndrome (HGPS). It occurs sporadically and has a strong racial susceptibility for Caucasians who represent 97% of these patients. Males are more affected with M:F ratio of 1.5:1. Both autosomal dominant and autosomal recessive modes of inheritance have been reported in literature. Recent genetic advances have detected de novo point mutations in lamin A (LMNA) gene located on chromosome 1q22 as the causative factor. LMNA encodes lamin A and C, which are the main components of intermediate filamentous lamina, function as a structural support and are essential for DNA replication and mRNA transcription. Prelamin A is a protein located on the nuclear membranes of cells, it needs to be cleaved to form lamin A, a process defective in patients with progeria. The increased prelamin A causes nuclear blebbing and altered shape of the nucleus. However, the mechanism by which the altered shape of the nucleus leads to symptoms of premature aging is not known till date. Based on the rapidity with which
Symptoms of premature aging appear, classical and non-classical forms of progeria are described. The rate of aging in affected children is accelerated by about seven times. Symptoms in HGPS are mainly related to the changes occurring predominantly in skin, musculoskeletal and cardiovascular system. Cutaneous manifestations are earlier to develop followed by skeletal and cardiovascular changes. Children with classical progeria, appear normal at birth, but within a year they begin to display the effects of accelerated aging. The dominant clinical manifestations include short stature; weight distinctly low for height; diminished subcutaneous fat (lipodystrophy); head disproportionately large for face; micrognathia; prominent scalp veins; generalized alopecia; prominent eyes; delayed and abnormal dentition; pyriform thorax; short, dystrophic clavicles; “horse-riding” stance; wide-based shuffling gait; thin limbs, and prominent, stiff joints; and failure to complete sexual maturation. Features frequently present are skin that is thin, taut, dry, wrinkled, and brown-spotted in various areas; sclerodermatous skin over the lower abdomen, proximal thighs, and buttocks; prominent superficial veins; loss of eyebrows and eyelashes; persistently patent anterior fontanel; sculpted, beaked nasal tip; faint nasolabial cyanosis; thin lips; protruding ears; absence of ear lobules; thin, high-pitched voice and dystrophic nails. Motor and mental development is normal. Radiological findings commonly seen include, normal bone age, diffuse osteopenia, bone resorption of distal phalanges and clavicles (acroosteolysis), fish mouth vertebral bodies, widened metaphysis, and attenuation of cortical bone thickness. In non-classical progeria, growth can be less retarded, scalp hair remains present for a longer time, lipodystrophy is more slowly progressive, osteolysis is more expressed except in the face, and survival well into adulthood is not uncommon. As children mature, this disorder causes them to age about a decade for every year of their life.(8) Differential diagnoses of HGPS include mandibulo-acral dysplasia, Werner syndrome, Cockayne syndrome and Hallerman-Streiff syndrome.

These children usually have severe atherosclerosis, and death occurs as a result of cardiac (myocardial infarction) or cerebrovascular disease (stroke), generally between age 5 and 20 years, with a median life span of 13 years. Cataracts and tumours have infrequently been noted, but many changes associated with normal aging in adults, such as presbyacuia, presbyopia, arcus senilis, osteoarthritis, senile personality changes, or Alzheimer disease, are not found.(5) There is no specific treatment for HGPS. The use of statins and bisphosphonates has resulted in reduced lipodystrophy, reduced hair loss, improved bone defects and enhanced longevity. Pravastatin and Zoledronic acid (a bisphosphonate) are the drugs that are presently being used in few countries for prevention of cardiovascular disease and osteoporosis respectively.(9)

**Conclusion**

HGPS is a rare disorder, with a complex pathogenesis and involves different organ systems. Despite being described as early as 1886, it was not until this decade that the precise cause of HGPS has been elucidated. Discovery of the genetic mutation causing HGPS has paved way for greater understanding of this disorder and also for exploration of newer treatment options. Improving the quality of life for these children is paramount. Minimizing invasive medical interventions, avoidance of regular pain, and adequate psychological support to patients and their parents and siblings are very important. A normal diet, accepting the severely impaired growth, non-surgical support of the limited joint mobility, sealing of teeth, and provision of wigs are simple and achievable goals that help patients and families to cope with the disorder. Finally, parents with an affected child, need to be reassured that since this disorder occurs due to a sporadic mutation the chances of its recurrence in subsequent pregnancies is extremely rare.

**References**