Progeria

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Abstract
Hutchinson-Gilford progeria syndrome is an extremely rare disorder characterized by premature aging of postnatal onset. The main clinical and radiological features include alopecia, thin skin, hypoplasia of nails, loss of subcutaneous fat, stiffness of joints and osteolysis. Intelligence is not impaired. Early death is caused by atherosclerosis or cerebrovascular disease, and failure to thrive. Most cases are sporadic, caused by a de novo *dominant recurrent truncating mutation within the lamin A gene. Numerous progeroid syndromes represent differential diagnoses for this entity.*

Keywords
Hutchinson-Gilford syndrome, premature aging, lamin A gene mutation

Disease name and synonyms

- Progeria
- Hutchinson-Gilford progeria syndrome (HGPS)

Progeria is a term recognized by many physicians as applying to individuals who appear prematurely aged. Misdiagnosis of HGPS is frequently made in patients presenting with some of the features of the syndrome, *i.e.* alopecia and skin with an aged appearance.

Prevalence

The estimated birth prevalence is one in four million births.

Diagnosis criteria / Definition

Association of:
- Prematurely aged phenotype of postnatal onset
- Rapidly progressive growth failure
- Characteristic facies, alopecia, loss of subcutaneous fat, hypotrichosis, thin, wrinkled skin with prominent superficial veins
- Stiffness of joints, osteolysis
- Early death by atherosclerosis or cerebrovascular disease

Clinical description

Clinical manifestations are evident by the first or second year of life. The failure to grow and to gain weight at a normal rate usually appears abruptly during the first year of life and can recur later at times of illness. Linear growth tends to be about half the normal rate, and shows no rapid increase at prepubertal or pubertal ages. The weight deficit is greater than the height deficit. By the time growth failure can be noticed, the patients usually have a cranium which appears to be large in comparison with the face and body. Intelligence and brain development is not impaired. The mean age of death is 14 years. This death is often secondary to coronary artery disease.

Consistent clinical features include lower weight and less subcutaneous fat, craniofacial disproportion, micrognathia, prominent scalp veins, alopecia, "plucked-bird" appearance, abnormal teeth, pyriform thorax, short clavicles, "horse-riding" stance, wide-based gait, coxa valga, thin limbs, prominent and stiff joints, and distal osteolysis.

Other anomalies frequently present in Hutchinson-Gilford progeria are thin, wrinkled, sclerodermatous and brown-spotted skin, hypotrichosis, absence of eyebrows and eyelashes, patent fontanels and sutures, beaked nose, circumoral cyanosis, thin lips, protruding ears with absent lobes, and dystrophic nails with short terminal phalanges.

Autopsy reports have described varying degrees of generalized atherosclerosis, mainly involving the larger arteries. Coronary occlusions with myocardial infarctions were found more frequently than cerebral vascular lesions. Nephrosclerosis was sometimes described.

Differential 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-Rautenstrauch 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. Werner syndrome and acrogeria can be also mistaken with HGPS.

Diagnostic methods

Diagnosis currently depends upon recognition of clinical and radiographic findings. The finding of the common *LMNA* truncating mutation could also be helpful in the diagnosis.

The characteristic radiological abnormalities are to be found in the skull, thoracic cage, long bones and phalanxes. The cranial bones tend to be hypoplastic and the fontanels and sutures remain open longer than expected. Wormian bones are common. Thinning and resorption of the distal clavicles is the most consistent abnormality to be found in the thorax. Narrowing of the posterior ribs is frequent. The long bones are slender with thin cortices. Severe coxa vara is a consistent finding, and moderate genu valgum is frequently present. The progressive bone loss from the distal phalanxes of the fingers and/or toes is one of the hallmarks of the disease.

Etiology

The etiopathogenesis of progeria has been slow to emerge. Extensive metabolic investigations have failed to detect the defect in HGPS. Growth hormone (GH) responses are normal, elevated GH level is frequent, with an elevated metabolic rate. No abnormality of thyroid, parathyroid, pituitary or adrenal gland function has been reported. There is a degree of insulinoresistance. Abnormalities of skin collagen and elastin have been described, with markedly elevated elastin and collagen type IV production. Skin cultures are sometimes difficult because of early cell death. Hyperlipidemia has never been very high or marked. Some authors suggested defective vitamin E metabolism, others demonstrated increased fraction of heat-labile enzymes and other altered proteins. One patient had an inverted insertion in the long arm of chromosome 1 in 70% of cells, which suggested that a gene for progeria may be located on chromosome 1. Studies of aneuploidy in skin fibroblasts of patients with HGPS showed that the rate was significantly higher than in controls, but without a significant pattern of chromosome-specific aneuploidy. Studies of the DNA maintenance indicate faithful transcription in HGPS. Another study showed reduced DNA repair in progeria cells.

In 2003, mutations in *LMNA*, the gene encoding Lamin A (1q21.2), have been evidenced. It is to date the only gene associated with HGPS, and point mutations are found in 90% of individuals. A recurrent *de novo* point mutation within exon G608G is found in most of the individuals, leading to abnormal splicing truncated protein. Individuals with the common mutation G608G present a remarkably similar phenotype, whereas patients with other point mutations have unusual phenotypes. Other individuals with HGPS have been found to have uniparental isodisomy of chromosome 1 and a deletion of the *LMNA* gene.

The protein product of this gene coats and organizes the interior surface of the nuclear envelope. Immunofluorescence of HGPS fibroblasts with antibodies directed against lamin A reveals that 40-50% of the cells show irregular

shape of the nuclear envelope. The common mutation appears to act as a dominant negative mutation affecting nuclear morphology. Interestingly, mutations in *LMNA* have also been reported in other conditions, named laminopathies, including autosomal dominant and recessive Emery-Dreiffus muscular dystrophy, autosomal recessive restrictive dermopathy, autosomal dominant dilated cardiomyopathy with conduction system defects, autosomal dominant Dunningam-type partial lipodystophy, autosomal dominant limb-girdle muscular dystrophy 1B, autosomal recessive Charcot-Marie-Tooth type 2B1, autosomal recessive mandibuloacral dysplasia and atypical Werner syndrome.

Genetic counseling

De novo dominant mutations have been evidenced in HGPS. Most cases are sporadic and mean paternal age is increased. The risk for the sibs of a proband is small, limited to the possibility of germinal mosaicism. Nevertheless, genetic counseling requires clinical expertise in order to rule out other differential diagnosis and therefore different mode of inheritance. Molecular analysis of the *LMNA* gene could be helpful in some cases. Parent to child transmission has never been observed since patients with HGPS do not reproduce.

Antenatal diagnosis

Antenatal early molecular diagnosis is available if the mutation has been identified in the proband, although the risk of recurrence is small, limited to the unlikely possibility of germline mosaicism in one of the parents. Careful ultrasound monitoring searching for intrauterine growth retardation could also be proposed, but normal growth cannot rule out the diagnosis with certainty since birth weight varies from 1 to 3.8 kg.

Management including treatment

No effective therapy is currently available to cure the disease. Nevertheless, symptomatic treatment should be proposed for all 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. The possibility of coronary artery bypass surgery or percutaneous transluminal angioplasty has been reported. Low doses of aspirin could be discussed in the prevention of heart attacks or stokes. Anesthetics should be used with particular caution. Non aggressive nutritional therapy was proposed in a study and slightly improved weight gain and growth. Combined nutritional therapy and GH treatment improved growth velocity, levels of growth factors and lowered the basal metabolism rate. Since delayed loss of primary teeth is common, extractions may be required to avoid crowding or development of two rows of teeth.

Unresolved questions

A unique consanguineous family with autosomal recessive HGPS and homozygous mutation within the Lamin A gene has been reported, with overlapping features with mandibuloacral dysplasia. Further reports should confirm the existence of an autosomal recessive entity in HGPS.

A patient was reported to have a neonatal form of HGPS, but this diagnosis is discussed since the postnatal character of the premature aging is part of the definition of HGPS.

Although patients with HGPS have an aged appearance, they usually do not demonstrate senile cataracts, senile presbycusis, presbyopia, arcus senilis, osteoarthritis, or senile personalities. This syndrome may only mimic certain aspects of the aging process.

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