Growth Hormone Deficiency

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Subdivisions of Growth Hormone Deficiency

- acquired GHD
- congenital GHD
- idiopathic GHD

General Discussion

Growth hormone deficiency (GHD) is a rare disorder characterized by the inadequate secretion of growth hormone (GH) from the anterior pituitary gland, a small gland located at the base of the brain that is responsible for the production of several hormones. GHD can be present from birth (congenital), resulting from genetic mutations or from structural defects in the brain. It can also be acquired later in life as a result of trauma, infection, radiation therapy, or tumor growth within the brain. A third category has no known or diagnosable cause (idiopathic).

Childhood-onset GHD may be all three: congenital, acquired, or idiopathic. It results in growth retardation, short stature, and maturation delays reflected by the delay of lengthening of the bones of the extremities that is inappropriate to the chronological age of the child.

Adult-onset GHD is most often is acquired from a pituitary tumor or trauma to the brain but may also be idiopathic. It is characterized by a number of variable symptoms including reduced energy levels, altered body composition, osteoporosis (reduced bone mineral density), reduced muscle strength, lipid abnormalities such as increased LDL cholesterol, insulin resistance, and impaired cardiac function. Treatment for GHD requires daily injections of recombinant human growth hormone (rHGH).

Patients with GHD that have no known cause are diagnosed as having idiopathic GHD. Genetic tests may reveal a congenital anomaly, but are often considered unnecessary after confirmation of GHD since they will have no effect on treatment. However, it is recommended that children be retested for GHD when they transition from pediatric to adult care since GH levels may normalize upon reaching adulthood. The level of GH considered normal for an adult is much lower than that for a child, especially one undergoing the pubertal growth spurt.

Signs & Symptoms

A child with GHD is usually of normal size at birth. In a few cases, the infant may become hypoglycemic (low blood sugar) during the newborn period. If male, the child may also have a small penis (micropenis). Later, children with GHD have delayed rates of development of facial bones, slow tooth eruption, delayed lengthening of long bones,

fine hair, and poor nail growth. They may also demonstrate truncal obesity, a high pitched voice, and delayed closure of the sutures of the skull, leaving open spaces called fontanelles.

Growth increments are the most important criteria in the diagnosis of GHD in children. Normal levels of growth usually follow a pattern, and if growth during a recorded six to twelve month period is within those levels it is unlikely that a growth disorder exists.

Growth in the first six months of life is usually 16 to 17 cm. and in the second six months approximately 8 cm. During the second year 10 cm or more is normal. Growth in the third year should equal 8 cm or more and 7 cm in the fourth year. In the years between four and ten, an average of 5 or 6 cm is normal. Ten percent decrease in these norms results in a growth velocity insufficient for the child to keep up on his or her growth curve. When that is recognized, even before the child has fallen to a significantly low percentile (1.2% = -2 SD), he/she should then be tested for abnormally low levels of growth hormone.

An individual who acquires GHD later in life presents more generalized symptoms. They may notice a relative increase in fat mass, especially abdominal and visceral, along with a decrease in muscle mass. Decreased energy levels, anxiety, and/or depression are also common. Lipid levels are also affected, resulting in an increase in LDL-cholesterol and triglyceride levels.

Causes

Congenital GHD results from genetic error, and may be associated with brain structure defects or with midline facial defects such as a cleft palate or single central incisor.

Several genetic defects have been identified:

Growth hormone deficiency IA is autosomal recessive and is characterized by growth retardation in utero. Affected children are small in relation to their siblings. The infant usually has a normal response to administration of human growth hormone (hGH) at first, but then develops antibodies to the hormone and grows into a very short adult.

Growth Hormone Deficiency IB is also autosomal recessive and is similar to IA. However, there is some growth hormone (GH) present in the child at birth and usually the child continues to respond to hGH treatments.

Growth Hormone Deficiency IIB and III are similar to IB, but IIB is autosomal dominant and III is X-linked.

Classic genetic diseases are the product of the interaction of two genes, one received from the father and one from the mother.

Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary to cause a particular disease. The abnormal gene can be inherited from either parent or can be the result of a new mutation (gene change) in the affected individual. The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy. The risk is the same for males and females.

Recessive genetic disorders occur when an individual inherits two copies of an abnormal gene for the same trait, one from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease but usually will not show symptoms. The risk for two carrier parents to both pass the defective gene and have an affected child is 25% with each pregnancy. The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The chance for a child to receive normal genes from both parents and be genetically normal for that particular trait is 25%. The risk is the same for males and females.

All individuals carry 4-5 abnormal genes. Parents who are close relatives (consanguineous) have a higher chance than unrelated parents to both carry the same abnormal gene, which increases the risk of having children with a recessive genetic disorder.

X-linked genetic disorders are conditions caused by an abnormal gene on the X chromosome and manifest mostly in males. Females that have a defective gene present on one of their X chromosomes are carriers for that disorder. Carrier females usually do not display symptoms because females have two X chromosomes and only one carries the defective gene. Males have one X chromosome that is inherited from their mother and if a male inherits an X chromosome that contains a defective gene he will develop the disease.

Female carriers of an X-linked disorder have a 25% chance with each pregnancy to have a carrier daughter like themselves, a 25% chance to have a non-carrier daughter, a 25% chance to have a son affected with the disease and a 25% chance to have an unaffected son.

If a male with X-linked disorders is able to reproduce, he will pass the defective gene to all of his daughters who will be carriers. A male cannot pass an X-linked gene to his sons because males always pass their Y chromosome instead of their X chromosome to male offspring.

Acquired GHD can occur as a result of many different causes including brain trauma (perinatal or postnatal), central nervous system infection, tumors of the hypothalamus or pituitary (pituitary adenoma, craniopharyngioma, Rathke’s cleft cyst, glioma, germinoma, metastases), radiation therapy, infiltrative diseases (Langerhans cell histiocytosis, sarcoidosis, tuberculosis), or, if without another diagnosis, it is considered idiopathic.

Affected Populations

Prevalence and incidence data vary widely due to the lack of standard diagnostic criteria. While congenital GHD and most cases of idiopathic GHD are thought to be present from birth, diagnosis is often delayed until the patient’s short stature is noticed in relation to their peers. Diagnosis most often occurs during two age ranges. The first is around 5 years of age when children begin school. The second is around 10-13 years old in girls and 12-16 years in boys associated with the delay in the pubertal growth spurt.

There is no apparent racial difference in the incidence of GHD. However, the National Cooperative Growth Study (NCGS), Genentech's now closed large North American database, revealed that 85% of patients receiving GH treatment for idiopathic GHD were white, 6% were black, and 2% were Asian. Similar distributions were seen with patients with other forms of short stature. In addition, patients from other racial groups tend to be shorter than their white counterparts at the time of diagnosis, reinforcing the assertion of, if not racial, a socio-economic disparity.

Growth hormone deficiency affects males and females equally except for GHD III which affects only males. However, given the greater concern for boys with short stature in most societies, diagnosis tends to favor males over females. 73% of patients with idiopathic GHD in the NCGS were male. Additionally, patients with GHD from organic causes such as tumors and radiation, in which no gender bias should be present, were still 62% male.

Related Disorders

Symptoms of the following disorders can be similar to those of Growth Hormone Deficiency. Comparisons may be useful for a differential diagnosis:

Small for gestational age (SGA) generally describes any infant whose birth weight and/or length was less than the 3rd percentile (adjusted for prematurity). Children with SGA are shorter and thinner than his or her peers. Typical characteristics for these children include low birth weight, short birth length, inadequate catch-up growth in first two years, persistently low weight-for-height proportion, and lack of muscle mass and/or poor muscle tone. The FDA has approved growth hormone therapy as long-term treatment of children who were born SGA and who have not achieved catch-up growth by two years of age.

Short stature homeobox-containing gene (SHOX) deficiency refers to short stature caused by a mutation in one copy of the SHOX gene and is associated with some cases of Turner syndrome, Leri-Weil syndrome and dyschondrosteosis. Growth hormone therapy is FDA-approved for SHOX deficiency.

Idiopathic short stature (ISS) is defined as having a height significantly shorter than the normal population (-2.25 SD, that is shorter than 1.2% of the population of the same age and gender), a poor adult height prediction (generally defined by having less than the calculated midparental height or, as a rough guide, less than 5'4″ for males and less than 4'11" for females), and no detectable cause for short stature. Growth hormone therapy is FDA-approved to treat ISS. Turner syndrome is a chromosomal disorder affecting 1 of 2,500 females and is characterized by short stature and the lack of sexual development at puberty. Other physical features may include webbing of the neck, heart defects, kidney abnormalities, and various other anomalies. Among affected females, there is also a heightened incidence of autoimmune disease such as Hashimotos's hypothyroidism and celiac syndrome. There appears to be great variability in the degree to which girls with Turner syndrome are affected by any of its manifestations since classical Turner, completely lacking one X chromosome, comprises only 60% of the total. The other 40% have a wide variety of genetic abnormalities including deletion of segments of the long or short arm of the X (or Y) and mosaicism with different

populations of cells. (For more information on this disorder, choose “Turner” as your search term in the Rare Disease Database.)

Noonan syndrome is a genetic disorder that is typically evident at birth (congenital) and is thought to affect approximately one in 1,000 to one in 2,500 people. The disorder is characterized by a wide spectrum of symptoms and physical features that vary greatly in range and severity. In many affected individuals, associated abnormalities include a distinctive facial appearance; a broad or webbed neck; a low posterior hairline; a typical chest deformity and short stature. Characteristic abnormalities of the head and facial (craniofacial) area may include widely set eyes (ocular hypertelorism); skin folds that may cover the eyes’ inner corners (epicanthal folds); drooping of the upper eyelids (ptosis); a small jaw (micrognathia); a depressed nasal root; a short nose with broad base; and low-set, posteriorly rotated ears (pinnae). Distinctive skeletal malformations are also typically present, such as abnormalities of the breastbone (sternum), curvature of the spine (kyphosis and/or scoliosis), and outward deviation of the elbows (cubitus valgus). Many infants with Noonan syndrome also have heart (cardiac) defects, such as obstruction of proper blood flow from the lower right chamber of the heart to the lungs (pulmonary valvular stenosis). Additional abnormalities may include malformations of certain blood and lymph vessels, blood clotting and platelet deficiencies, mild mental retardation, failure of the testes to descend into the scrotum (cryptorchidism) by the first year of life in affected males, and/or other symptoms and findings. Noonan syndrome is an autosomal dominant genetic disorder which may be caused by abnormalities (mutations) in a number of genes, four of which are PTPN11, KRAS, SOS1 and RAF1. (For more information on this disorder, choose “Noonan” as your search term in the Rare Disease Database.)

Prader-Willi syndrome (PWS) is a genetic disorder characterized by low muscle tone, short stature, incomplete sexual development, and a chronic feeling of hunger that, coupled with a metabolism that utilizes fewer calories than normal, can lead to excessive eating and life-threatening obesity. The food compulsion makes constant supervision and food restriction necessary. Average IQ is 70, but even those with normal IQs almost all have learning issues. Social and motor deficits also exist. At birth the infant typically has low birth weight for gestation, hypotonia (weak muscles) with difficulty sucking which can lead to a diagnosis of failure to thrive. The second stage (“thriving too well”), has a typical onset between the ages of two and five, but can be later. The hyperphagia (extreme unsatisfied drive to consume food) lasts throughout the lifetime. Younger children with PWS have sweet and loving personalities, but this phase is also characterized by increased appetite, weight control issues, and motor development delays. As the child becomes older, there are more behavioral problems and medical issues. (For more information on this disorder, choose “Prader-Willi” as your search term in the Rare Disease Database.)

Primary growth hormone insensitivity (GHI), also known as Laron syndrome, is a group of extremely rare genetic disorders in which the body is unable to use the growth hormone that it produces. GHI can be caused by mutations in the growth hormone receptor gene or mutations in genes involved in the signaling pathway within the cell after growth hormone binds to its receptor, preventing production of insulin-like growth factor (IGF-1), the intermediary hormone responsible for the growth effects of growth

hormone. Children with GHI who are treated with IGF-1 before puberty have improved growth, but, unlike children with growth hormone deficiency given growth hormone treatment, they do not have normal growth restored.

GHI is characterized by normal or high levels of circulating growth hormone, delayed bone age and onset of puberty, prominent forehead, low blood sugar and obesity in adulthood. Except for an extremely rare form of GHI, where the gene for IGF-I is defective, brain development is normal but some may have mild intellectual impairment. (For more information on this disorder, choose “primary growth hormone insensitivity” as your search term in the Rare Disease Database.)

Standard Therapies

Testing is very important in determining whether the child with growth retardation does indeed have growth hormone deficiency. Various agents may be used including insulin (hypoglycyemia), arginine, clonidine and l-dopa. These tests are meant to stimulate the pituitary to secrete GH allowing for the testing of blood samples for the levels of GH at timed intervals.

Physicians often test for other hormone deficiencies that may be the underlying cause of short stature. FreeT4, TSH, cortisol, celiac antibodies, etc. are measured to ensure they are within normal levels and deficiencies must be normalized with appropriate therapy before GHD can be diagnosed.

IGF-1, a protein produced primarily by the liver but present in all tissues in response to GH stimulation, can be measured to screen for GHD and later to titrate GH therapy.

Children with severe GHD should be re-tested after completing growth to see if they meet the requirements for GH therapy as an adult.

When a diagnosis of GHD is made, treatment may then be initiated. Children with GHD should be started on recombinant human growth hormone as soon as the disorder is recognized to optimize growth potential. The dosage is gradually increased to its highest during puberty, and discontinued at or near completion of skeletal maturation when the patient may require retesting to see if GH is needed as an adult.

The FDA has approved the use of somatropin (Nutropin [Genentech)] Humatrope [Lilly], Genotropin [Pfizer], Saizen [EMD Serono], Norditropin [Novo Nordisk], Tev-Tropin [Teva], and Omnitrope [Sandoz] for the treatment of growth hormone deficiency.