Growth Hormone Deficiency and Chromosome 18 Abnormalities

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There have been many questions over the past several years about growth hormone deficiency: what is it , how is it determined, how would treatment help my child? We are providing this information in the hope that parents will better understand the issues involved in this complex subject. This will help you make informed decisions about your child's health.

Your child's growth should be carefully tracked on a growth chart. The growth chart permits your child's height to be compared to that of a large population of normally growing children. For example, if your child's height is located on the growth chart at the 50th percentile, this means that 50%, or one half, of children of that age are taller than your child and 50% of children of that age are shorter than your child. Normally growing children can be at any percentile on the growth chart. A child whose height is at the 2nd percentile and who is growing normally will stay with the growth curve at the 2nd percentile month after month or year after year. Beyond 2 years of age, normal growth is not happening when a child changes percentiles. For example, if a child has a length at the 50th percentile at 2 years of age, the 25th percentile at 3 year of age and the 5th percentile at 4 years of age, this child is failing to grow normally.

Your child's change in height over a period of time is called his/her growth velocity. An average growth velocity will keep your child at the same height percentile over a period of time. If your child maintains a height which is at the 2nd percentile over a period of time, your child may be short, but your child's growth velocity is normal and it is unlikely that your child has a growth problem.

The average child grows 8 - 10 inches in the first year of life, 4 - 5 inches in the second year of life and 2 - 3 inches in the third year of life. Growth velocity, beyond age 3 gradually declines, reaching its slowest rate at about 9 1/2 years in girls and 10 1/2 years in boys. Subsequently, the sex hormones transiently accelerate growth, with an average growth rate reaching 3 inches per year at age 11 1/2 in girls and 4 inches per year at age 13 1/2 in boys. This acceleration is generally referred to as the pubertal growth spurt. Following the pubertal growth spurt, the rate rapidly declines. Most girls have reached their adult height by 14 1/2 years and boys by 17 1/2 years of age.

You can estimate a child's expected adult height (if your child did not have a chromosome abnormality) by calculating the mid-parental height.

For girls: $\frac{\text{(father's height - 5 inches) + mother's height}}{2}$

For boys: $\frac{\text{(father's height + (mother's height +5 inches)}}{2}$

This gives a rough range, plus or minus 2 inches, of your child's expected adult height. The predicted height can then be placed on the growth chart to determine which percentile of adult height has been predicted. If your child is growing normally, the current height of your child should be near the predicted percentile.

Rough estimates of adult height can also be obtained by taking a boy's length at age 2 and a girl's length at age 18 months and doubling them. In a normally growing child, this adult height estimate should be close to the mid-parental height estimate.

There are 7 major categories of causes of short stature. They are:

1. Familial: Short parents are more likely to have a short child than are tall parents.

2. Constitutional delay or "late bloomer": Children who are going to go through puberty later than other children are often small, even during early childhood; however they "catch up" by the time puberty is completed.

3. Chronic disease: These include inflammatory bowel disease, chronic kidney failure and cyanotic heart disease. Children with these problems often grow poorly because of under-nutrition, decreased tissue response to various factors or interference of drugs with growth.

4. Chromosomal/genetic: The mechanism of poor growth and short stature is not known for most chromosomal/genetic conditions. Short stature and poor growth has been associated with chromosomal abnormalities such as Down syndrome and Turner syndrome.

5. Hormonal: The primary hormones affecting growth are thyroid hormone and growth hormone. Under production of either of these substances can result in poor growth.

6. Psychosocial: Growth hormone production is greatly affected by input from the brain. For example, abnormal sleep cycles decreases growth hormone production. The best described examples are in children who live in socially chaotic homes and children in "warehouse" orphanages.

7. Intrauterine growth retardation: The growth of some infants is stunted even before they are born. For example, a full term infant who weighs four pounds would be stunted.

Familial short stature and constitutional delay account for the largest percentage of determined causes. Although chromosome abnormalities and pituitary deficiency are listed as two different causes, a child with a chromosome abnormality could be short due to an endocrine problem.

One of the treatable causes of short stature is growth hormone deficiency. The medical specialist who evaluates children for growth hormone deficiency is a "pediatric endocrinologist." Evaluation to determine if a child is growth hormone deficient involves not only checking levels of growth hormone in the blood, but also by closely monitoring the effects of growth hormone on the body. Evaluation for growth hormone deficiency involves many different measurements. A pediatric endocrinologist would want to personally measure your child's height over a period of time, usually for at least 6 months. These height/length measurements will then permit your child's growth velocity to be calculated. The importance of sequential measurements using standard growth charts cannot be over emphasized. Growth rates below the 25th percentile for age warrant further investigation.

It will also be important to measure your child's bone age (bone maturation.) When a child is born, much of the skeleton is made of cartilage. This cartilage changes to bone in a predicable manner throughout childhood. The rate of physical development corresponds better with bone maturity than with chronologic age. A bone age is usually

determined by obtaining an x-ray of the left hand and wrist and comparing this x-ray to standards for normal bone. A child with familial short stature would have a bone age which is the same as his/her chronological age. A child with growth hormone deficiency would have a bone age which is significantly delayed compared to his/her chronological age.

Growth hormone is produced by the pea sized pituitary gland at the base of the brain. Growth hormone is a peptide hormone and not a steroid hormone. Most growth hormone is released by the pituitary gland during nighttime sleep in 3 -5 short pulses. Growth hormone is in the blood stream for a short time; however it causes other organs in the body to produce growth factors (e.g., IGF-1 and IGFBP-3) which remain in the blood stream at a more constant level. The simplest, but indirect method, for examining growth hormone production is to determine the levels of these growth factors in the blood.

The more difficult way to measure growth hormone is to directly stimulate the pituitary gland with a drug which causes growth hormone to be released. The actual test is done as follows: 1) a blood sample is taken to determine the initial (unstimulated) levels of growth hormone; 2) the growth hormone stimulant is given; 3) blood samples are taken every 15 - 30 minutes for about 2 hours. A normal response to the test would be an initially low level of growth hormone which rises sharply after the stimulation is given (growth hormone sufficiency.) An abnormal response would be to show no or minimal increase in the growth hormone level. Unfortunately 5-10% of normal children will fail to respond to any single stimulation test, and some children will give a normal response even though they do not produce normal amounts of growth hormone on a daily basis. For these reasons, duplicate stimulation tests are usually performed with different stimulants. The chance of obtaining an inaccurate result on two different tests is much smaller.

A more reliable indicator of growth hormone production would be to measure the blood levels every 20 minutes over a 24 hour period. In theory, this type of growth hormone testing would provide an indication of the child's actual ability to produce growth hormone naturally. However, the act of taking blood every 20 minutes could alter the normal sleep cycle which could affect the normal pattern of growth hormone production. Also, this testing procedure is very complex and expensive; therefore it is not used very often.

If a child is found to be growth hormone deficient, replacement therapy can be started. Growth hormone is given by daily injections under the skin (subcutaneously) using a small insulin type syringe and needle. Parents are trained to prepare the growth hormone for injection (most forms come as a powder) and to give the injections to their children. There are devices into which the syringe can fit which make giving an injection easier. Often children can learn to give their own injections. Growth hormone treatment is usually continued until an x-ray shows that the bones are no longer capable of growing . For girls this is at about age 16 and for boys this occurs at about age 18.

Recently, the Food and Drug Administration has given approval for the use of growth hormone replacement therapy in adults who are growth hormone deficient. There is also considerable research into alternatives to treatment by daily injection. They include monthly injections and oral medications. This opens the door for life-long treatment, with the possibility that treatment will not be by daily injection.

Aside from increasing height, growth hormone has been shown to be important to normal wound healing, muscle tone and fat metabolism [Strobl and Thomas, 1994]. Growth hormone has also been used in AIDS patients to slow wasting and to help restore both weight and strength [Schambelan et al, 1996; Waters et al, 1996].

Use of growth hormone therapy in individuals who are deficient has few side effects. More than 50,000 children have been treated with growth hormone, and it has proven to be a safe treatment for growth hormone deficiency. Certain medical problems have been associated with growth hormone treatment. Whether these problems are caused by growth hormone treatment is not known. The problems may be related to the process of growing, or the child may have developed the problem even if he/she was not been treated with growth hormone. If a large group of growth hormone treated children are evaluated, these problems seem to occur more often than they do in the general population. In some cases the natural rate of occurrence of these problems in the pediatric population is not known. Some of these problems may come to a physicians attention because growth hormone treated children are seen by physicians on a more regular basis than are other children.

Problems which occur with increased frequency (albeit low) in growth hormone treated children include:

1. Increased pressure inside the skull (benign intracranial hypertension.)
2. Slippage of the growth plate on the head of the long bone of the upper leg (slipped capital femoral epiphysis.)
3. Changes in the level of thyroid hormone or alterations in the function of the thyroid gland (hypothyroidism.)

Each of these conditions will be explained to you in depth by your pediatric endocrinologist if your child is placed on growth hormone replacement therapy. It is important to understand that the possibility of any of these events occurring in any particular child is very small.

Historically, growth hormone was in very short supply. It was extracted from collections of "pea-sized" human pituitary glands taken from cadavers. Consequently, it took many pituitary glands to produce small amounts of the hormone. Because of the short supply, use of this natural growth hormone was rationed by the National Pituitary Agency and was approved for use only in children who had no other health problems (or major chromosome abnormalities.) In 1983 growth hormone made by recombinant DNA techniques became available. This provided an almost unlimited supply of growth hormone; however, the cost remained very high, producing a rationing by cost instead of supply. The increased availability of growth hormone allowed more widespread use of growth hormone in clinical trials for short stature syndromes (e.g. Turner, Noonan, Prader-Willi, Down and 18q- syndrome) and children with short stature due to chronic illness.

Growth hormone treatment has also been used in children with Turner syndrome and Down syndrome. Children with these syndromes are usually short, but they are not growth hormone deficient.

Children with the 18q- syndrome are often short which can be due to growth hormone deficiency [Schwarz and Duck, 1990; Andler et al., 1992; Ghidoni et al., 1997]. In our own unpublished data, 34 children with 18q- were tested for growth hormone deficiency. Sixty six percent were found to make insufficient amounts of growth

hormone. Those children who have started growth hormone replacement therapy have responded to the treatment and are growing at a greatly increased rate compared to their pretreatment rates.

There are several reports in the literature of patients with 18p- who were growth hormone deficient [Leisti et al., 1973; Andler et al., 1992; Buffoni et al., 1976; Artman et al., 1992; Schober et al., 1995]. A survey of Registry families who have children with 18p- showed that 13 out of the 16 children whose parents returned the questionnaire were abnormally short. Several of the respondents had children who were babies and were, therefore, too young to have post-natal growth failure. Of those 13 short children, 11 had been tested for growth hormone deficiency and 7 of those children were on growth hormone replacement therapy. The other 4 of the 11 who had undergone growth hormone testing were not deficient. Therefore, from this small survey it appears that a great majority of children with 18p- are abnormally short and, of the short children tested for growth hormone deficiency, 64% were growth hormone deficient. All of the children on growth hormone replacement therapy are responding well to treatment.

Since individuals with Ring 18 have deletions of both the long arm and the short arm, they are also at risk for being growth hormone deficient. There are two reports in the literature of individuals with Ring 18 who were growth hormone deficient [Abusrewil et al., 1988; Meloni et al., 1994].

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