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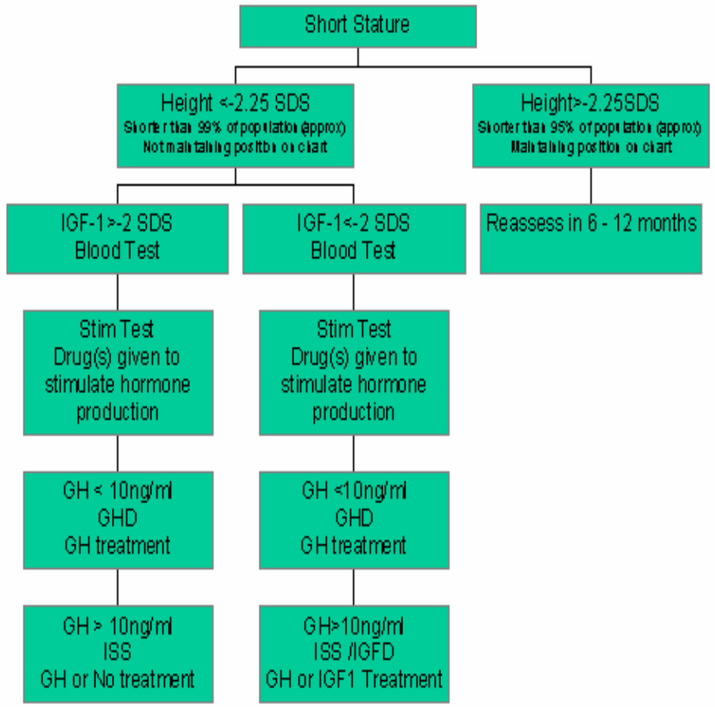
Adapted from Pediatric Endocrine Reviews (PER) Volume 4, Supplement 4: May 2007



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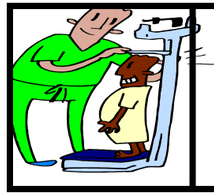

The Diagnosis & Treatment of Idiopathic Short Stature

The MAGIC Foundation

July 2007

Growth failure may occur throughout childhood. Fifty years after the first injection of growth hormone was administered to an extremely short child the scientific and medical community are still debating the best way to diagnose and classify growth disorders to help them find the most appropriate treatment. The availability of a new drug treatment called Insulin Like Growth Factor 1 (IGF1) has opened up further debate concerning the diagnosis and treatment of growth disorders.

There are a number of factors that families should be aware of when discussing their child's growth with their Pediatric Endocrinologist:

1. Diagnosing a growth disorder is like a jigsaw puzzle. To complete the puzzle you need all of the pieces in the correct place . Unless you get the pieces just right they will not fit.
2. Just like a puzzle, the growth disorder diagnosis has a process that must be followed before the puzzle comes together. As you progress through the puzzle the options narrow and the choices are easier easy to make. We have tried to describe the process for you on page 4 of this newsletter.
3. One of the most complex diagnoses made in a growth assessment today is the diagnosis of Idiopathic Short Stature (ISS) - the definition of which is 'the patient is short and we do not know why'. The issue with this diagnosis is ' how do you treat the child with this diagnosis'? Do you treat them with growth hormone for a period of time or do you consider a newer option such as IGF1?

In this update we will attempt to walk you through the latest diagnostic techniques for the evaluation of short stature and suggest some ideas for discussing the issues with your Doctor.

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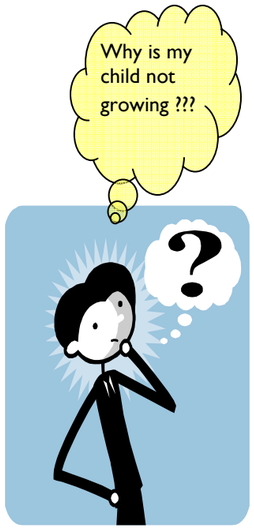
So let's take a simplified look at the way the body secretes and uses hormones to help it grow.

The easiest way to think about the hormone system is to look at it like the mechanics of a toilet system. When the toilet is flushed the valve releases water to fill the tank. When the tank is full the flapper shuts off the water supply automatically. This is exactly how the hormone system works. Your body tells the glands to produce a hormone (stimulating hormone). When the body has enough of the hormone another hormone (inhibitory hormone) shuts off the supply similar to shutting off the water supply in the toilet. One of the main hormones that helps people grow is growth hormone (GH). Normal growth hormone levels after childhood are equally important for maintaining bone strength and helping metabolism.

It used to be thought that GH worked directly on the growth plates to make bones grow. Research in recent years suggests that it is likely that GH works through a system called insulin like growth factors (IGF's) to reach the growth plates. Insulin like growth factors are very important for bone and tissue growth. The discovery of IGF's and their role in the growth of children has the world of endocrinology discussing new ways to diagnose and treat growth disorders.

See Page 2 & 3 for details about IGF's



Current issues in the diagnosis of Idiopathic Short Stature (ISS)

The term ISS was originally used to describe a growth problem that occurs when all known causes of growth failure have been ruled out. Recent scientific and medical advances have led the endocrine community to take another look at this unexplainable diagnosis.

Perspectives on Idiopathic Short Stature was published in May, 2007 in Pediatric Endocrine Reviews (PER) . Volume 4, Supplement 2, suggests that some children that may have been diagnosed as ISS really have issues with IGF secretion. (see page 3 for description of IGF secretion). About half of the children diagnosed with ISS in a recent clinical trial proved to have a low IGF1 level and met the diagnostic criteria for IGFD.

This dilemma leads us to consider alternative treatments for ISS today. In a society where many people do not believe in treating ISS, they consider it a cosmetic issue. Is it now possible that there is an underlying IGF problem which like any other hormone issue should be adequately addressed?

There are many things for families to consider when discussing this information with your pediatric endocrinologist. Here are two things to consider :

1. If your child is short and a cause can be found such as IGFD or GHD then treating the cause of the problem with the appropriate hormone makes sense. You should check with your endocrinologist to see if your child has a deficiency of any of these hormones.
2. If your child has a diagnosis of ISS and is on GH treatment and its working well—great, leave well alone! If GH is not working well then you should discuss the possibility of IGF treatment with your Doctor.

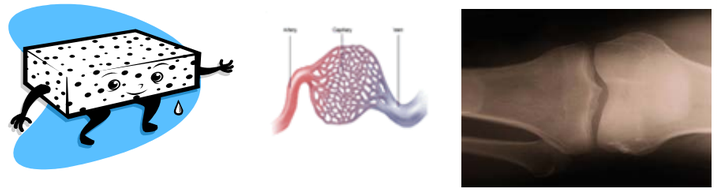
Terminology Cheat Sheet

Name	Abbreviation	Description
Growth Hormone	GH	Necessary for growth—commercially available
Growth Hormone Deficiency	GHD	Does not produce enough GH
Growth Hormone Resistant	GHR	You produce enough GH but the cells of the body resist its action
Insulin like Growth Factor	IGF	A number of factors that work to stimulate bone growth
Insulin Like growth Factor binding protein	IGFBP	The part of the cell which IGF sticks to allow it to be used by the body
Insulin like Growth Factor 1	IGF1	A growth factor that stimulates bone growth—commercially available
Insulin like Growth Factor Resistance	IGFR	A state where the body produces enough IGF 1 but the body resists accepting it
Primary Insulin like Growth Factor Deficiency	IGFD	A blood IGF level of < -2SDS for the a child of the same age and sex. (A very low amount of IGF in the blood)
Standard Deviation Score	SDS	Describes the distance from the population 'norm' in a measurement

Schematic of GH and IGF

GH Is secreted by the pituitary gland

After GH is secreted from the pituitary gland (located at the base of the brain) it is carried through the blood stream attached to the blood by 'binding' to a ' receptor' on the cell surface. When the IGF's have been transported to the bone they are released and absorbed by the growth plates to produce bone growth. Think of this like a bath sponge soaking up water through the holes in it surface. When the sponge arrives at the growth plate it squeezes out the water so it can be used. When the sponge dries out the body sends a message back to the brain to produce more hormone.



GH binds to the cell and is carried by the blood stream to its target organ

Insulin like Growth Factors (IGF's) are present in nearly all of the body's cells (building blocks) and play a important role in cell growth and survival. Simply put, they help your body grow. As in most hormone abnormalities, IGF's can be measured in the blood. There are a range of normal IGF values for both sex and age. It is important when you look at your blood results not to be confused by the ranges (numbers) that the laboratory call "normal". Ask your Pediatric Endocrinologist to explain the results and what they mean for your child.

Recent discussions about the diagnosis of IGFD center around classifying the different types of IGF deficiency or resistances. Here is my interpretation of the current thinking. Primary IGFD, defined as the underlying cause of the deficiency, lies at the cellular (building block) level. Secondary IGFD occurs due to either a GH secretion or GH transport problem. Secondary IGFD may also occur as a result of a chronic illness.

How will you know what the cause of the IGFD is and does it matter?

Currently, the treatment is for Primary IGFD is IGF treatment and for secondary IGFD is growth hormone. Academic discussions are ongoing with regard to possibly treating secondary IGFD with IGF in the future. Your pediatric endocrinologist is the best person to make sure that you have the necessary tests that provide them with the all pieces of the puzzle to make sure that your child gets the best treatment option available.

Monitoring Treatment Progress

There are a number of things to be considered when looking at treatment progress with either GH or IGF1.

How do you know if its working?

- Everyone has there own idea of success— my definition of success with a growth treatment is to double the pre treatment growth rate in the first six months on therapy. For example if your child grew 0.5 inches in the six months before treatment started then you may expect to see 1 inch or more in the first six months after starting treatment. (always check with your Dr about the expectations for therapy results). For treatment to be successful , the dose needs to start right and be adjusted every 4 to 6 months to keep up with your child's growth (both in weight and height) and most importantly should be given every day as ordered by your Doctor.
- Apart from measuring height and weight and body composition the Dr will also monitor the amount of IGF 1 circulating in the blood. The aim of this is to keep the IGF level at the mid to high range of normal by adjusting the drug dosage.
- Last but not least comes the question—when should you consider changing the type of treatment? In my personal opinion if the current treatment is working, leave well alone—but if the response is not as expected then consider either a reassessment of the disorder and ask your pediatric endocrinologist about alternative treatment options.