INSULIN-LIKE GROWTH FACTOR I DEFICIENCY

The mission of the Human Growth Foundation is to help children and adults with disorders related to growth or growth hormone through education, research, support and advocacy. The Human Growth Foundation is dedicated to helping better understand the process of growth and the treatment of growth disorders. Its objectives are:

- Support of research
- Family education and service
- Public education
- Education of healthcare professionals

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This booklet is dedicated to the group of patients with severe IGF-I deficiency who were first treated with recombinant human IGF-I.

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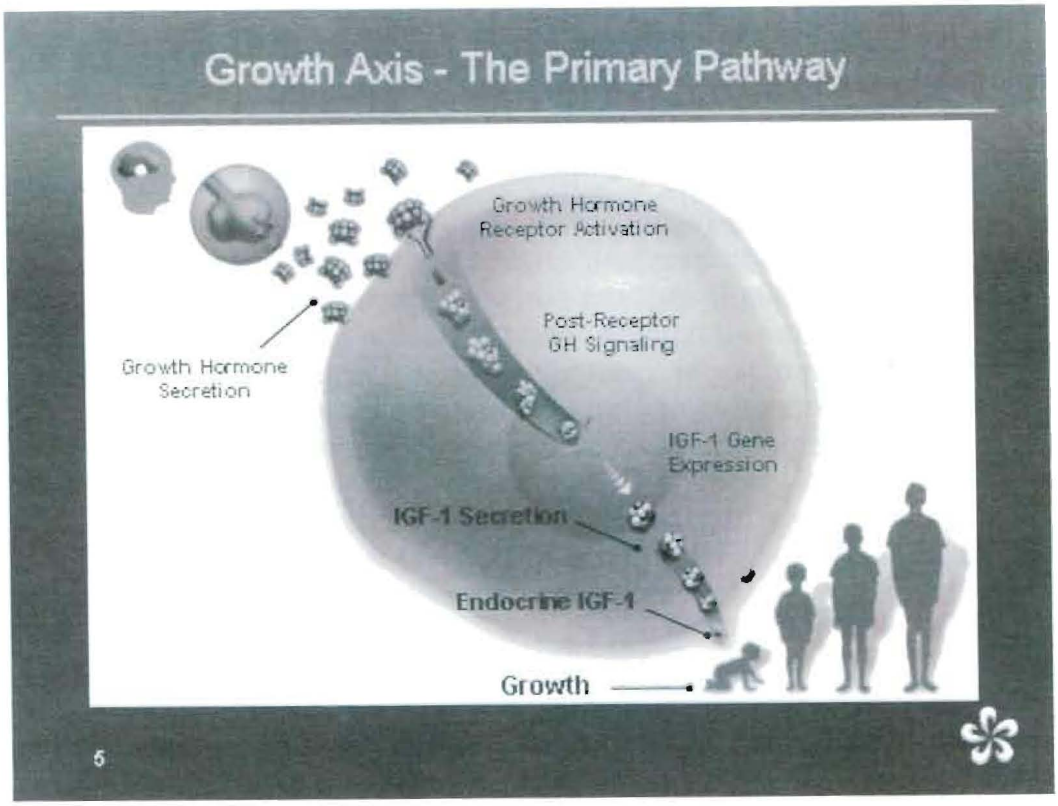
INSULIN-LIKE GROWTH FACTOR-I DEFICIENCY

Growth is the process of change in body size that accompanies the physical maturation children and adolescents undergo between birth and adulthood. The majority of children grow at normal rates and will attain adult heights in the same range as their parents. Most children – even the ones growing near the lower growth curves – do not have a growth problem. On the other hand, some children are growing at a slower-than-normal growth rate, and this is an important clue that an underlying anomaly or disease is at play. A child who grows slower than normal may indeed have a serious health problem, regardless of the height at any specific point in time. Still, most children who grow below their genetic potential may not have true growth failure, but may represent variations of normal growth (e.g. late maturers/late bloomers). A minority of children present with true growth failure due to an underlying condition which, if untreated, will lead to short stature in adulthood. This booklet deals with one of the causes of growth failure: deficiency of insulin-like growth factor I, or IGF deficiency.

THE GROWTH HORMONE – IGF-I – GROWTH PLATE AXIS



"Incorporating 'Growth Axis — The Primary Pathway', by permission of Tercica, Inc."

THE GROWTH HORMONE – IGF-I – GROWTH PLATE AXIS

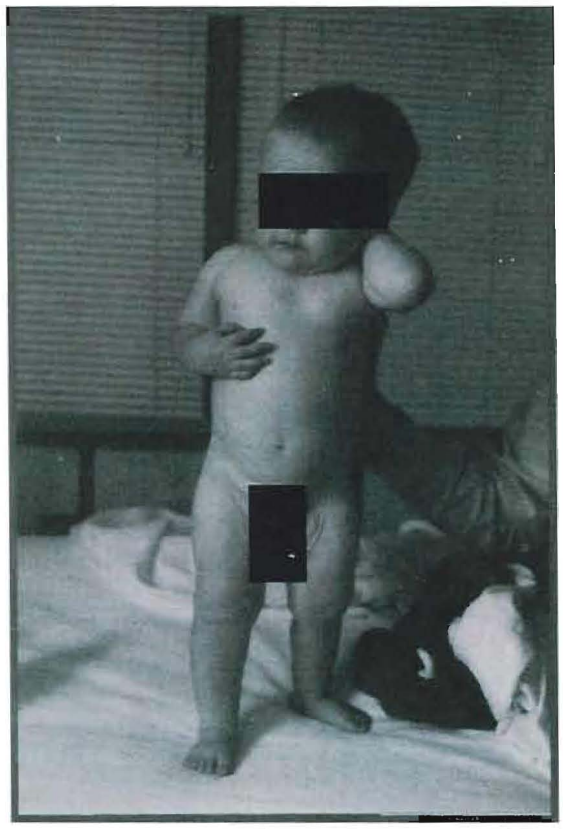
Growth is a strong indicator of an individual's general health, both physical and mental. The growth of an individual is determined by his or her environment, genetic background, nutrition, overall health status, and the production of certain chemicals called hormones. Hormones are produced by the cells of the endocrine glands. In the classical sense, hormones will be released into the bloodstream, then travel to different organs and tissues in the body (including the skeleton), where they will exert their effect.

There are multiple hormones involved in the growth process. One of the major growth-promoting hormones is growth hormone. Growth hormone is secreted by cells in the anterior pituitary gland, which is a pea-sized gland located at the base of the brain, below an extension of the brain called the hypothalamus. The secretion of growth hormone by the pituitary gland is in response to chemical stimuli from both the brain and the hypothalamus. After secretion, growth hormone then travels through the body, via the circulation, to exert its action at the different target tissues. Part of our bodies' growth is purely dependent on these direct effects of growth hormone itself. However, the majority of the growth-promoting action of growth hormone is exerted via another hormone, called insulin-like growth factor-I (IGF-I). After growth hormone reaches some of its target organs, it will bind to growth hormone receptors on specific cells. This growth hormone binding to its receptor causes a series of chemical reactions within the cell that lead to the production of IGF-I. In response to growth hormone, IGF-I is produced locally in many tissues and is also released into the blood from the liver. Circulating IGF-I and locally synthesized IGF-I act at the epiphysis (bone growth plate) to cause enlargement of the bone (growth). IGF-I itself has a strong growth-promoting effect and it is estimated that approximately two-thirds of all growth is due to the effects of IGF-I directly.

CAUSES OF IGF-I DEFICIENCY

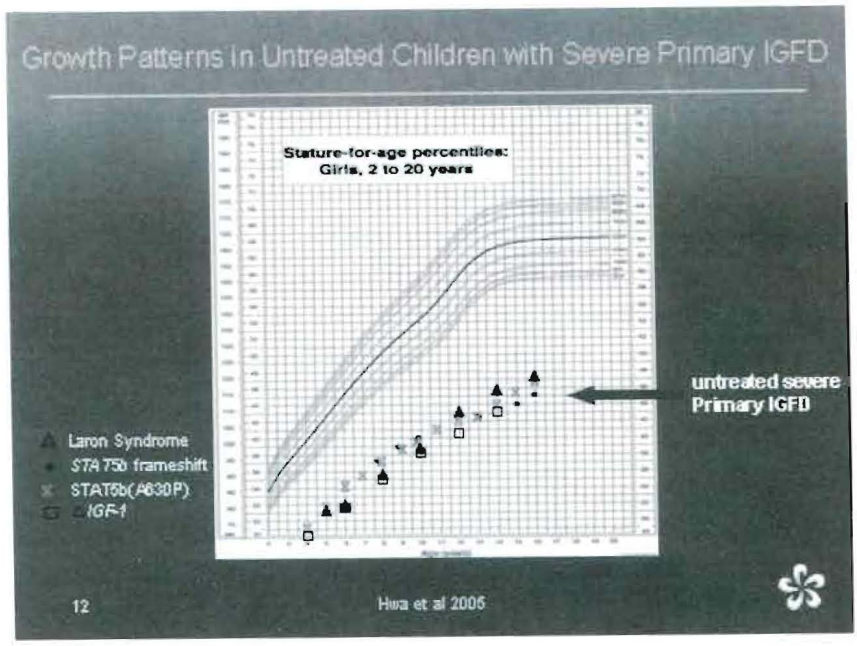
IGF-I deficiency has also been called growth hormone insensitivity syndrome or growth hormone resistance syndrome. IGF-I deficiency was first described in a severe form, due to a block of growth hormone action at the level of the growth hormone receptor. As a consequence of this abnormal growth hormone receptor function, little IGF-I is produced. The ensuing severe IGF-I deficiency causes a type of growth failure that resembles the growth failure seen in patients with severe growth hormone deficiency. However, patients with severe IGF-I deficiency have normal concentrations of growth hormone (measurable in the blood). This primary form of severe IGF-I deficiency is differentiated from secondary forms of IGF-I deficiency or growth hormone insensitivity, caused by, for example, malnutrition or liver disease.

There are also patients with less severe forms of IGF-I deficiency. These patients may have milder forms of growth hormone resistance, or less severe decreases in IGF-I production due to milder cellular defects in the synthesis of IGF-I. Such patients will also have abnormal growth and short stature, but the degree of growth failure is less pronounced than in the former group with severe IGF-I deficiency. Some of the patients with milder forms of IGF-I deficiency have, in the past, been grouped in the category of patients with so-called idiopathic short stature (ISS). This name is used for children who have short stature without a specific diagnosis or explanation. As researchers are discovering more genetic abnormalities of the different growth hormones/growth factors, it is conceivable that some of the patients with idiopathic short stature will end up being diagnosed with mild or partial forms of IGF-I deficiency.



CLINICAL FEATURES OF SEVERE IGF-I DEFICIENCY

- Near-normal birth weight with slightly decreased length at birth.
- Severe growth failure after birth.
- Delayed bone maturation.
- Delayed puberty.
- Facial features include prominent forehead, small face, shallow orbits, blue sclera, and delayed dental eruption.
- Small children with IGF-I deficiency have an increased tendency to develop low blood sugars.
- Walking and other motor development may show delay.
- Tendency for excess fat deposition around the trunk.



Study entitled "Severe Growth Hormone Insensitivity Resulting from Total Absence of Signal Transducer and Activator of Transcription 5b. Vivian Hwa, et. al. JCEM 90(7):4260-4266 (2005)
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DIAGNOSIS OF IGF-I DEFICIENCY

Making a correct diagnosis of severe IGF-I deficiency is not always easy. The basis for the diagnosis of IGF-I deficiency is careful measurement of the patient's height, weight, and growth velocity. If the patient has severe short stature, or an abnormal growth deceleration, other diseases that could cause growth failure should first be ruled out. These diseases include disorders of the skeleton, under-nutrition and malabsorption, liver, lung, or kidney disease, thyroid hormone deficiency or other endocrine diseases such as rickets.

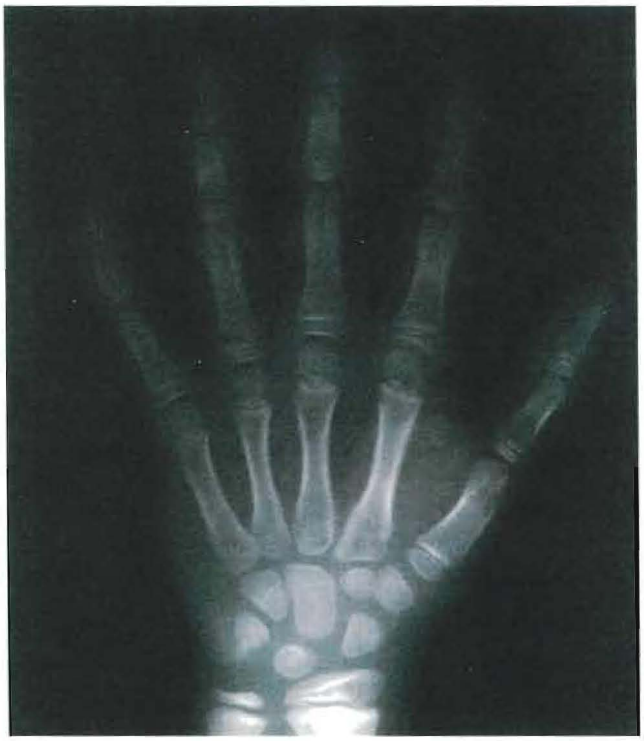
At this time, the evaluation should include an x-ray of the left hand and wrist for determination of the skeletal (growth plate) maturation.

Further laboratory evaluation should also include the measurement of IGF-I in the blood. This is done in association with the measurement of IGFBP-3, which is a carrier for IGF-I in the body. Finding a low IGF-I concentration and/or low IGFBP-3 may be an indication of growth hormone deficiency. Because of this, two growth hormone stimulation tests are usually done, and the results of this testing will indicate, in case of primary IGF-I deficiency, that the patient is able to make normal amounts of growth hormone.

The combination of low concentration of IGF-I (and IGFBP-3) with increased concentration of growth hormone is then highly suggestive of a diagnosis of growth hormone insensitivity or severe IGF-I deficiency. A final confirmatory test consists of the administration of growth hormone to the patient, for five to seven consecutive days, with determination of IGF-I concentrations before and after the growth hormone administration. Specific criteria will allow the physician to interpret the rise (or lack thereof) of

IGF-I with this procedure. The diagnosis of severe IGF-I deficiency can be made this way, but it is much more difficult to use this test for the diagnosis of a milder form of IGF-I deficiency. This is because specific ranges for a patient's sex and age of IGF-I responses have yet to be determined.

Growth Plate Film



Patient undergoing growth hormone stimulation testing at the bedside.

TREATMENT OF IGF-I DEFICIENCY

More than ten years of experience with IGF-I treatment of patients with severe IGF-I deficiency has shown that IGF-I can promote growth in these patients. This has led to the recent United States Food and Drug Administration (USFDA) approval of IGF-I as a therapeutic agent for severe forms of IGF-I deficiency. Specifically, IGF-I is approved in the United States for the long term treatment of growth failure in children with severe primary IGF-I deficiency, or with severe growth hormone deficiency plus development of antibodies to growth hormone (which cause the administration of growth hormone to be ineffective). Shortly after the approval of IGF-I, a second product was also approved by the USFDA: a combination of IGF-I with IGFBP-3 (IGF-I/BP-3 complex).

IGF-I is produced by recombinant DNA technology. The synthetically produced IGF-I is identical to that of the human IGF-I produced in the body. The IGF-I made by recombinant DNA technology is synthesized in bacteria that have been modified through the addition of the genetic information for human IGF-I, so that IGF-I can be produced in a purified preparation in large quantities. IGF-I is administered, using a sterile disposable syringe and needle, in the subcutaneous tissue. The doses of IGF-I are individualized for each patient, and the prescribing endocrinologist will determine both the dosage and administration for each patient. IGF-I needs to be administered two times per day, usually at the time of food intake (for example, at breakfast and at supper). The reason for this timed administration is because of the potential glucose lowering effect of IGF-I. The injections also need to be rotated to a different site with each administration.

Treatment with IGF-I is usually carried out over several years, until the patient reaches adult height, or the maximum growth potential is achieved. The growth response to IGF-I therapy in patients with severe IGF-I deficiency is less than the response observed in growth hormone deficient patients treated with growth hormone. Although the precise explanation for this phenomenon is unclear, it is possible that the continued lack of direct growth hormone effect plays a significant role in this less-than-optimal growth response.

SAFETY OF IGF-I THERAPY

One concern of IGF-I therapy relates to the insulin-like properties of IGF-I itself. In patients with severe IGF-I deficiency, the development of low blood glucose can be seen. This is why the IGF-I is administered in conjunction with a meal.

Lipohypertrophy, which means thickening of the fat tissue under the skin, can also be seen if the injections are not properly dispersed.

Less common adverse events include intracranial hypertension, which is an increase of the pressure in the head, and usually leads to nausea and vomiting in the early morning hours. Although rare, this is a serious adverse event, and the occurrence of it needs to be detected early. Increased intracranial pressure disappears when the IGF-I treatment is discontinued. The treatment can usually be restarted without recurrence. Other less common adverse events include lymphoid tissue hypertrophy, which may occasionally lead to an increased frequency of middle ear infections, snoring, and may require removal of tonsils and adenoids.

FUTURE DEVELOPMENTS

Ongoing research with recombinant human IGF-I throughout the United States is currently underway. This research is both directed at evaluating the safety and efficacy of IGF-I, as well as its applicability in children with milder forms of growth failure due to milder forms of IGF-I deficiency. At this time, the use of IGF-I in these patients is investigational. Clinical trials to evaluate once-a-day dosing of IGF-I are also underway.

Although the USFDA has also approved the combination product of IGF-I and IGFBP-3, its clinical use for the treatment of growth failure associated with severe IGF-I deficiency has been halted. This is due more to legal and regulatory issues related to patent legislation, rather than to clinical factors.

Further investigational use of IGF-I will also focus at combining its administration together with recombinant human growth hormone, as well as for its potential role related to the other functions of IGF-I in the body's metabolism.

The Human Growth Foundation is a non-profit organization that is nationally recognized as an information and support resource for individuals and families affected by growth disorders and growth hormone deficiency. The Human Growth Foundation helps to:

- Educate the public about growth problems
- Refer children with growth problems for evaluation
- Provide information about growth problems to affected families
- Provide guidance for the physical, psychological, and social development of children with growth problems
- Help short children learn to cope with living in a bigger world
- Co-sponsor research on growth
- Raise funds for all of the above activities

You can obtain more information about the Human Growth Foundation activities by contacting the national office in writing: Human Growth Foundation, 997 Glen Cove Avenue, Suite 5, Glen Head, NY 11545. The Human Growth Foundation telephone number is 1.800.451.6434. Alternatively, you can also visit the Human Growth Foundation website at www.hgfound.org.

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