

# Complications of growth hormone therapy in children

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The introduction of human growth hormone (GH) prepared by recombinant DNA technology has resulted in increased numbers of children and adults receiving treatment. This trend has led to questions concerning the safety of GH, particularly when used for indications other than GH deficiency. This review discusses the effects of GH on fluid, lipid, and carbohydrate metabolism; the risk of intracranial hypertension or pseudotumor cerebri; the effects on the skeletal system; the risk of malignancy; and the effects on the immune system. At present, GH treatment appears to be safe, although long-term follow-up of GH-treated patients is necessary.

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The use of recombinant DNA technology to produce human growth hormone (GH) has resulted in a marked increase in availability of GH to treat short stature due to GH deficiency (the major indication) and other conditions, such as chronic renal insufficiency (the other approved indication in the United States), Turner's syndrome (an approved indication in 26 countries), idiopathic short stature, and adult GH deficiency. The increased use of GH for both traditional and nontraditional indications has raised questions concerning the safety of GH treatment. What follows is a review of the most recent literature on possible adverse effects of GH.

## Edema, cerebral edema (pseudotumor cerebri), and fluid and electrolyte homeostasis

### Sodium and water balance

Acute treatment of GH-deficient adults with GH leads to sodium and water retention with increased plasma renin activity and aldosterone levels [1]. The symptoms can include hypertension, dependent edema, and carpal tunnel syndrome [2,3]. In a study of 50 elderly men selected for GH treatment on the basis of low levels of insulin-like growth factor-I, Cohn *et al.* [3] observed 10 cases of carpal tunnel syndrome, four of which were asymptomatic. The onset of signs or symptoms of carpal tunnel syndrome was variable and associated with insulin-like growth factor-I levels greater than 1 U/mL. Carpal tunnel syndrome seems to be less common in younger adults treated with GH [2,4,5], and it has not been reported in GH-treated children. One possible explanation for this difference lies in the fact that GH secretion in healthy individuals is age dependent, peaking during puberty and declining thereafter. Thus, what is defined as a "replacement" dose of GH

in a child may in fact represent a pharmacologic dose for an elderly adult.

Two recent papers studied the effect of GH on the renin-angiotensin-aldosterone axis in children [6,7]. Barton *et al.* [6] observed a transient, slight, but statistically significant increase in blood pressure during the 1st week of treatment. This effect was present both in children with diminished GH secretion and those with idiopathic short stature. There was no significant edema or increase in body weight, suggesting that water retention was minimal. There was no clinically significant hypertension. Plasma renin and aldosterone levels remained within the normal range. DiMartino-Nardi *et al.* [7] studied the effect of GH on blood pressure, height, weight, plasma renin activity, aldosterone, and atrial natriuretic peptide in children with idiopathic short stature. They found no difference in these parameters in GH-treated children compared with untreated control subjects. Because their first observation occurred 3 months after the start of GH, they might not have seen the transient changes described by Barton *et al.* [6]. In any case, hypertension, dependent edema, and clinically significant fluid retention do not seem to be major problems in children treated with GH [5].

### Idiopathic intracranial hypertension (pseudotumor cerebri)

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, has been reported in 22 children throughout the world who received biosynthetic GH for a variety of indications [8]. The diagnoses include GH deficiency (seven cases), chronic renal failure (eight cases), Turner's syndrome (two cases), Prader-Willi syndrome (two cases), and delayed puberty (one case). In two cases, the indication for GH treatment was unknown. Signs of IIH developed within 8 weeks of the start of GH therapy in 13 cases. In six cases, the interval was longer (2 to 60 months). Res-

### Abbreviations

GH—growth hormone; IIH—idiopathic intracranial hypertension; SCFE—slipped capital femoral epiphysis.

olution of papilledema and other symptoms occurred when GH treatment was discontinued. In some patients, GH was continued at lower doses, with resolution of IIH.

Idiopathic intracranial hypertension is uncommon in children [9,10<sup>\*</sup>]. In a study from the University of Iowa, there were 30 cases of IIH in children documented over a 30-year period from 1960 to 1990 [10<sup>\*</sup>]. IIH was more common in children older than 10 years of age, and the incidence was equal in boys and girls. This finding is in contrast to adults, in whom women of reproductive age have a much higher incidence of IIH than men. Obesity is a risk factor for IIH in children as well as in adults. Thirty-three percent of the children in the Iowa study had weights that were greater than the 95th percentile for age. Renal disease is a known risk factor for IIH [11–13]. It is therefore interesting to note that eight children treated with GH for renal disease developed IIH, in contrast to seven children treated for GH deficiency. Although the exact numbers of children worldwide who receive GH for these two indications are unknown, it is almost certain that many more children are receiving GH for the latter indication, and children with renal disease treated with GH may have a greater risk of developing IIH. Other risk factors for the development of IIH are chronic glucocorticoid treatment or a rapid tapering thereof; certain antibiotics, particularly tetracyclines; vitamin D deficiency; vitamin A excess; hypoparathyroidism; thyroid disorders [14]; and treatment of long-standing hypothyroidism [15–17]. A previous febrile illness may also predispose to IIH [10<sup>\*</sup>].

Headache is the most common presenting complaint in children with IIH. Blurred vision or diplopia, nausea, and vomiting are also commonly reported. Sixth nerve palsy seems to be much more common in children than in adults [10<sup>\*</sup>]. The initial evaluation of a child with suspected IIH should include examination of the optic discs and cranial nerve function, including visual field testing, and computed tomographic or magnetic resonance imaging studies to determine if there is a mass lesion. Neuroimaging studies in children with IIH will be normal or show decreased ventricular size. A lumbar puncture with an increased opening pressure (obtained after neuroimaging studies have excluded the presence of a mass lesion) will confirm the diagnosis of IIH. In many cases, the lumbar puncture will also relieve symptoms.

Because visual loss is the most important complication of IIH, all children with IIH should have careful neuroophthalmologic follow-up. If there is no severe visual loss at presentation and no significant deterioration in vision, medical management, including discontinuation of GH with reinstitution of treatment at lower doses and repeated lumbar punctures as indicated by recurrence of symptoms, may be helpful. If the initial lumbar puncture was accompanied by clinical improvement, glucocorticoids and carbonic anhydrase inhibitors, such as acetazolamide, may be tried. Optic nerve sheath fenestration is the preferred surgical treatment if there is severe visual loss or deterioration of visual fields [9,10<sup>\*</sup>].

## Disorders of carbohydrate metabolism

Growth hormone has long been known to decrease insulin sensitivity. Children with severe GH deficiency often present in infancy with hypoglycemia that responds to GH replacement, and patients with acromegaly can have both carbohydrate intolerance and overt diabetes mellitus. Insulin resistance induced by GH is due to a postreceptor defect [18]. Adults with both untreated GH deficiency and diabetes mellitus have a decreased risk of developing the long-term complications of diabetes [19]. As the indications for GH use have widened, there has been continuing concern about possible adverse effects of GH treatment on carbohydrate metabolism, particularly in patients, such as girls with Turner's syndrome, in whom there is an increased risk of non-insulin-dependent diabetes [20].

In an international survey of over 8100 children receiving GH, there were 12 children with diabetes mellitus [21]. Of these, two acquired type II diabetes during GH treatment (one of these children was obese and had a family history of type II diabetes), eight had preexisting type I diabetes, and one had had transient diabetes of the newborn prior to developing insulin-dependent diabetes while receiving GH. Recurrence of diabetes in children previously thought to have transient diabetes of the newborn has been observed in other infants not treated with GH [22]. Only one child developed type I diabetes mellitus after receiving GH. Although the incidence of both type I and type II diabetes differs from country to country, it does not appear that GH treatment is associated with an increased incidence of symptomatic diabetes mellitus in the absence of other predisposing factors. There has been another case report of hyperglycemia in an obese child treated with GH for severe familial short stature [23]. If an obese child has a predisposition to type II diabetes, it may be wise to monitor glucose tolerance before and during GH therapy.

Girls with Turner's syndrome frequently have insulin resistance, which can be worsened by GH even though their carbohydrate tolerance is normal [24]. In a study that compared the growth-promoting effects of recombinant GH with those of oxandrolone in girls with Turner's syndrome, insulin and glucose responses were determined fasting and 2 hours after a standard glucose load. In this study, oxandrolone rather than GH was associated with abnormalities of carbohydrate metabolism [25]. A German study of the long-term effects of GH alone in Turner's syndrome found carbohydrate intolerance in 9.7% of the girls prior to GH treatment [26]. Girls receiving higher doses of GH (3 or 4 U/m<sup>2</sup>/d) had statistically significant increases in insulin, although glucose levels and hemoglobin A<sub>1c</sub> remained normal. Girls receiving the lowest dose of GH had a transient increase in integrated insulin concentrations at 3 months. One obese patient in the highest dose group developed glucose intolerance with elevated insulin levels after 12 months of GH therapy. It appears as if most girls with Turner's syndrome are able to maintain normal carbohydrate tolerance during GH treatment at the price of hyperinsulinemia. Because hyperinsulinemia itself may be associated with deleteri-

ous effects on blood lipids, it is probably wise to monitor carbohydrate tolerance and serum lipids in these girls, particularly if there is marked obesity or a strong family history of type II diabetes.

Adults with GH deficiency have an increased age-adjusted risk of death from cardiovascular events, and GH is known to affect serum lipoprotein levels. GH treatment increases hepatic receptors for low-density lipoproteins, thus increasing their clearance and decreasing serum low-density lipoprotein levels [5,27]. The effects of GH on serum lipids, if significant, are likely to be beneficial.

### Slipped capital femoral epiphysis and other musculoskeletal disorders

In the general population, slipped capital femoral epiphysis (SCFE) is most common in adolescents [28]. Obesity and trauma, which may be mild, are thought to predispose to the development of slipping. The typical patient is an overweight adolescent boy with delayed puberty. Studies in experimental animals suggested that GH treatment decreases the force necessary to cause slipping, probably by increasing the width of the femoral growth plate [29]. There have been a number of reports of an association between GH treatment and SCFE. In 1985, Rappaport and Fife [30] surveyed the occurrence of SCFE in GH-deficient children before, during, and after GH treatment. Although the data in this paper do not provide information on the incidence of SCFE in this population, they do suggest that GH deficiency itself, as well as GH treatment, may be associated with an increased risk. This suggestion is supported by a French study, which reported follow-up data on over 5400 patients treated with GH (most with pituitary GH). There were six reported cases of hip problems (femoral osteochondritis as well as SCFE) found prior to GH therapy and seven cases that occurred during GH treatment [31]. Other studies also indicate that SCFE is not uncommon in GH-deficient children prior to treatment [32,33].

Since the approval of biosynthetic GH, reports of SCFE in children treated with this product have appeared [34,35]. In two cases, there was subsequently an SCFE on the opposite side [34]. Because 20% to 25% of children who have a slip on one side develop slipping on the contralateral side, this finding is probably to be expected. Most authors recommend getting radiologic studies of both hips in patients with SCFE [36]. Complaints of limping or hip or knee pain should be evaluated carefully in GH-deficient children whether or not they are receiving GH treatment at the time.

Dupuytren's contracture (flexion deformity of the fingers resulting from thickening of the palmar fascia) occurs in acromegaly. There is a single case report of Dupuytren's contracture in a child who received GH for radiation-induced hypopituitarism [37].

A French survey of patients treated with both pituitary and biosynthetic GH reported 47 cases of scoliosis,

most of which occurred in patients who had received spinal radiation or had undergone neurosurgical procedures [31]. There is one report of a patient with panhypopituitarism who began replacement treatment with GH at the age of 22 years who developed rapid progression of preexisting scoliosis during GH treatment [38]. Progression of idiopathic scoliosis is known to be associated with rapid growth such as occurs during puberty, and thus it is difficult to determine if it is GH itself, apart from its effects on growth, that is responsible for progression of scoliosis.

### Occurrence and recurrence of neoplasia

#### Risk of leukemia

The possible effect of GH in inducing malignancy or promoting the growth of a preexisting tumor has been one of the areas of greatest concern [39]. For a variety of reasons, it is also a difficult area to study. Reports from Japan of an increased incidence of leukemia in patients treated with GH prompted a careful assessment of this question [40,41]. Data were collected from several national registries. Not surprisingly, the results and conclusions differ. Fradkin *et al.* [42] surveyed 6284 American recipients of human pituitary GH with 83,917 person-years of risk and found six cases of leukemia (expected, 2.26 cases). Although this increased risk was significant, there was no increased risk of leukemia in patients with idiopathic GH deficiency (one case found). The increased risk was confined to subjects with a previous cranial tumor (four craniopharyngiomas, one astrocytoma). Furthermore, four of the subjects had received radiotherapy. It was suggested that craniopharyngioma might be associated with an increased risk of leukemia. Because four of the five patients with craniopharyngioma who developed leukemia had received radiotherapy, it is unclear whether it is the tumor itself or its treatment that is associated with the increased risk.

The relative risk figures obtained by Japanese workers have been revised downward [43]. However, these authors still find an increased risk that is associated with idiopathic GH deficiency rather than GH deficiency secondary to a preexisting tumor and its treatment. The Japanese data are interesting in that four of the eight children with idiopathic GH deficiency who developed leukemia had acute myelogenous leukemia, and one had malignant histiocytosis. (Also of interest is the fact that this child had evidence of a virus-associated hemophagocytic syndrome on bone marrow studies prior to the diagnosis of malignant histiocytosis.) One of the patients with acute myelogenous leukemia had anemia and low leukocyte count 2 months prior to beginning GH therapy. Only three children developed acute lymphoblastic leukemia, which is the most common form of leukemia in children.

This difference in the type of leukemia is particularly intriguing in view of the association of Fanconi's anemia with GH deficiency [44]. Not all children with Fanconi's anemia will have characteristic physical anomalies, such as radial hypoplasia. Because patients with Fanconi's anemia have an increased risk of develop-

ing leukemia (greater than 50% by the age of 40 years, with two thirds of these cases presenting under the age of 20 years) and because in one third of patients the leukemia is not preceded by detectable bone marrow failure, some of the increased risk of acute myelogenous leukemia found in patients who received GH may be due to the inclusion of patients with unrecognized Fanconi's anemia rather than to an effect of GH treatment [45\*].

Other long-term surveys of patients treated with pituitary GH [31,46] have not found an increased incidence of leukemia in patients treated with GH. At present, the conclusion that "The risk, if any appears to be small" [41] remains valid. Furthermore, the most recent studies [42,43] indicate that the relative risk of a GH-treated patient developing leukemia is decreased below that previously calculated [41].

There continue to be individual case reports of other tumors occurring in GH-treated patients [47,48]. At present, it is not possible to determine if GH treatment had a role in the development of these unusual tumors or if other, as yet unidentified risk factors were present. Of note, neither the French [31] nor the American survey [42] found any increased risk of lymphoma in GH-treated individuals.

### **Tumor recurrence and second malignancies**

Children treated for malignancy have a 10-fold increase in their risk of developing a second tumor [49]. Radiation, genetic factors, and chemotherapy singly or in combination are known to predispose a patient to develop a second malignancy. In a survey of 308 second malignancies that occurred in 292 subjects treated for childhood cancer, there were 14 patients in whom no known risk factors were present who nevertheless developed a second tumor [49]. This is one of a number of reasons why it is impossible to evaluate the effect of GH treatment on the occurrence of second malignancies and on tumor recurrence in general. Other reasons include the lack of large databases of children treated under the same standard protocol, the use of different doses of chemotherapy and radiotherapy at different centers, and continuing changes in treatment protocols. For tumor recurrence, differences in the nature of the initial malignancy will also affect the chances of recurrence.

A review of an international database containing data from 258 children treated with GH for hypopituitarism secondary to a craniopharyngioma (1338 patient-years at risk) found 17 recurrences (6.6%). Four of these children had also had tumor recurrence prior to starting GH therapy and might be expected to have a greater risk of relapse [50].

A smaller survey of recurrence of medulloblastoma in GH-treated children showed a relative risk of 0.82 compared with children who did not receive GH (95% confidence interval, 0.28 to 2.37). In a British study of brain tumor recurrence [51], 16 of the 47 children had residual abnormalities on computed tomography prior to starting GH therapy. Of these 16, two later had a recurrence while receiving GH [51-53].

Although there have been individual reports of relapses in patients with leukemia after prolonged remissions [54], larger surveys [53] do not report an increased incidence of relapse in leukemic children treated with GH while in remission. Because the risk of relapse after a prolonged (longer than 5 years) remission is small, it would require a large database to detect a slight increase in risk that could be ascribed to GH treatment.

### **Growth of nevi**

The incidence of melanoma in young adults has been increasing, although malignant melanoma remains uncommon in children [55\*]. There are a number of risk factors for the development of melanoma, of which intense, intermittent sun exposure in a fair-skinned person is the most important one subject to modification. An increased number of acquired nevi (also a result of intense sun exposure and severe sunburn) is also a risk factor. Typically, the number of such nevi increases in childhood, to a peak in the 3rd and 4th decades, and then decreases [55\*]. A recent study monitored the growth, but not the number, of pigmented nevi in children treated with GH for either GH deficiency or Turner's syndrome [56]. GH increased the growth rate of the nevi twofold. Nevi from both GH-treated and control children were excised for the usual clinical indications of location or abnormal appearance. All were histologically normal. However, the nevi taken from children treated with GH were more likely to bind an antibody (HMB-45) that labels actively growing melanocytes. Thus, GH appeared to stimulate melanocyte growth.

In a study of 39 girls with Turner's syndrome treated with GH and estradiol, an increase in the number and size of nevi was noted in one patient after 3 months of GH therapy. At the next follow-up, most of the nevi had bleached and disappeared [57].

In a study that combined nevus diameter and irregularity of contour to give an "index of atypia," there was no statistically significant difference in the mean index of atypia between girls with Turner's syndrome on GH treatment and control groups with and without recent sun exposure [58]. However, the authors of this paper thought that some nevi in GH-treated girls might have been affected by GH, whereas most were not. Although the effect of GH on growth of nevi merits careful observation, particularly in girls with Turner's syndrome who are prone to have increased numbers of nevi, excessive sun exposure remains the most important known (and preventable) cause of melanoma.

### **Growth hormone and the immune system**

In experimental animals, GH has been shown to have important effects on the development of the immune system. In humans, clinically significant defects in immune function are reported only in patients with X-linked GH deficiency and hypogammaglobulinemia. Although GH treatment may result in subtle and often inconsistent changes in laboratory tests of immune

function, no clinically significant symptoms of immune dysfunction have been reported either in GH-deficient children or after GH treatment [59]. A study of GH treatment in surgical patients did find a statistically significant decrease in the number of postoperative infections in the treated group [60].

## Conclusions

Growth hormone replacement therapy for GH deficiency was long thought to be completely safe. The finding that some patients who had been treated with pituitary GH as children later developed Creutzfeldt-Jakob disease as a result of that treatment [61] stunned the endocrine community and awakened it to the need for long-term follow-up of patients even after GH treatment had ceased. There is now evidence that GH treatment can have beneficial effects even after the potential for increased stature is passed. Use of GH in GH-deficient adults will increase the importance of careful follow-up. Fortunately, the data available at present support the statement that "human recombinant GH seems to be a remarkably safe drug when used in conventional substitution doses" [62]. Long-term follow-up of large numbers of patients remains critical to identify the magnitude of the risks of suspected adverse events related to GH treatment and to recognize new events if they occur.

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