Safety of Growth Hormone Treatment

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ABSTRACT

Growth hormone (GH) is being used in the treatment of GH deficiency and in the treatment of other conditions with increasing frequency. Several uncommon potentially adverse events including idiopathic intracranial hypertension (IIH), slipped capital femoral epiphysis (SCFE), increase in the number of pigmented nevi, gynecomastia, scoliosis, insulin resistance and a possible increase in malignancy have been associated with GH treatment. Despite its potential adverse effects, GH has had a good safety record up to now. This review will focus on the potential side effects of GH treatment in GH and non-GH deficient conditions.

Conflict of interest: None declared

INTRODUCTION

There has been a dramatic increase in the use of exogenous growth hormone (GH) for treatment since biosynthetic recombinant human GH (rhGH) became available in 1985. At present, besides GH deficiency, children with a wide variety of growth disorders are receiving GH treatment. Supraphysiological doses of GH are being used in non-GH deficient growth disorders.(1) Moreover, the action of GH via its receptor involves many organ systems and metabolic pathways and for this reason, the safety of GH treatment has become a major concern of issue in recent years. The aim of this paper is to review the potential side effects of GH treatment in different disorders treated with GH.

SODIUM AND WATER RETENTION

Side effects of GH treatment like peripheral edema and hypertension which may be seen in adulthood are rarely encountered in childhood.(2) Fluid retention and carpal tunnel syndrome are rare in children.

IDIOPATHIC INTRACRANIAL HYPERTENSION

Idiopathic intracranial hypertension (IIH) is defined as intracranial hypertension in the absence of a space occupying lesion and is characterized by increased cerebrospinal fluid (CSF) pressure with normal CSF composition, bilateral papilledema, visual changes, headache, nausea and vomiting. The incidence in childhood is 1/100,000.(3) IIH has been reported following GH treatment not only in patients with GH deficiency, but also in chronic renal insufficiency (CRI), Prader Willi syndrome (PWS) and Turner syndrome (TS).(4, 5, 6) The pathogenesis of IIH occurring with GH treatment may be due to its effects on body fluid distribution.
and resultant changes in fluid balance. Alternatively or in addition, GH may cross the blood brain barrier and increase local levels of insulin like growth factor-I (IGF-I) which in turn increases CSF production from the choroid plexus. (2) Large pharmacoepidemiological surveys have revealed an increase in IIH upon GH treatment (5, 7, 8) and reported frequencies ranging from 81 to 120/100,000. It is likely to occur in patients with CRI, TS, organic GH deficiency and PWS. (7) IIH has been associated with some medications (L-thyroxine, glucocorticoid, vitamin A and D) as well as with obesity, anemia, uremia and female gender. The onset of IIH is generally seen within a short period time (~2-12 weeks) after start of GH therapy, but it may also be seen months later. The signs and symptoms of IIH usually disappear and clinical improvement may occur within weeks or months after discontinuation of GH therapy. Symptoms usually do not reappear after reinitiating GH in low doses, probably due to homeostatic adjustment. (9) Loss of visual acuity or visual fields is a serious permanent complication of IIH.

ORTHOPEDIC PROBLEMS

Slipped capital femoral epiphysis (SCFE) is a disorder of the femoral head growth plate leading to a displacement of the femoral head epiphysis from its normal alignment. The incidence ranges from 2 to 13/100,000 individuals between 7 and 17 years of age. (10, 11) It may be associated with obesity, trauma, rapid growth, endocrine disturbances including hypothyroidism, hypogonadism and GH deficiency. (12) In GH deficiency, the growth plates are wide and this may result in weakness even without GH treatment. GH contributes to the widening of the weakest zone of the epiphyseal plate and thus may increase the risk of SCFE in GH deficient children treated with GH. (13) Pain in the hip or knee and limp are the major symptoms of SCFE and X-ray of the hip is the best diagnostic tool.

Treatment consists of correcting the displacement of the epiphysis with continuation of GH therapy recommended after orthopedic evaluation. (14)

The incidence of SCFE on GH treatment in pharmacoepidemiological surveys and national databases varies between 4 to 272 /100,000 and is higher than the incidence in the general population. (7, 15, 16, 17, 18, 19) However, it is difficult to assess the risk of SCFE in the general population because it varies with age, sex, race, geographical location and season. GH deficiency itself may cause SCFE and there may be other risk factors such as obesity, delayed skeletal maturation or other hormone deficiencies. Children with organic GH deficiency, TS and CRI are more prone to SCFE. (7) Obesity is a risk factor in these diagnostic groups.

The incidence of Perthe’s disease on GH treatment which may occur in GH deficient children independently of GH therapy does not seem to be increased on GH treatment compared to the general population (~5-7/100,000). (2)

Idiopathic scoliosis is most often seen in early adolescence and is more frequent in girls. Scoliosis is seen in ~4% of healthy school children. The frequency of scoliosis on GH treatment does not seem to be increased, (20, 21) but progression of scoliosis may be rapid. (2, 20) Some diagnostic groups like TS and PWS are prone to scoliosis. (17, 21, 22) It is increased during any period of rapid linear growth and is not independently correlated with GH therapy. (17, 20) Follow up is needed in risk groups.

CARBOHYDRATE METABOLISM

There has been a concern for the potential for induction of glucose intolerance or type 2 diabetes regarding GH treatment especially in children with disorders such as TS, CRI and low birth weight (children born small for gestation age-SGA). All of these disorders are known to be associated with abnormalities in carbohydrate metabolism. GH acts as an
insulin antagonist. Nearly all studies of GH therapy in children show an increase in insulin levels but normal glucose tolerance.\(^{(23, 24)}\) One pharmacoepidemiological study demonstrated an increased frequency of type 2 diabetes in children receiving GH approximately six-fold higher than previously reported incidence figures.\(^{(25)}\) However, other long term databases have been reassuring.\(^{(24, 26, 27, 28)}\) A large multicenter GH-postmarketing surveillance study reported diabetes or impaired glucose tolerance in approximately 1% of GH treated patients with CRI.\(^{(18)}\) SGA born short children show insulin resistance on GH treatment which resolves after discontinuation of GH therapy.\(^{(29)}\) Although published data form large postmarketing databases for GH treated children born SGA do not report adverse events,\(^{(5, 17, 21, 30)}\) more long term follow up of carbohydrate metabolism is needed in these groups of children.\(^{(31)}\) The long term consequences for prolonged hyperinsulinemia remain unclear.

### Malignancy

GH has been shown to increase the risk of malignancy in \textit{in vitro} and animal studies\(^{(32)}\) and it may increase the risk of cancer in humans.\(^{(33, 34)}\) Thus, another concern has been the malignant transformation on GH treatment. In initial reports, increased incidence of leukemia in GH recipients has been reported.\(^{(35, 36)}\) However, careful evaluation of national and multinational databases has not shown a significant increase in the risk of leukemia associated with GH therapy unless risk factors such as cytotoxic chemotherapy, genetic or hematological conditions or radiotherapy are present.\(^{(5, 18, 37, 38)}\) Relapse of leukemia has not been increased in database analyses.\(^{(5, 36, 37, 38, 39, 40, 41)}\) There is no increase in risk of developing a new extracranial nonleukemic neoplasm in GH recipients either.\(^{(42, 43)}\) Regarding tumor recurrences in GH treated patients with brain tumors, data from single and multicenter studies\(^{(39, 44, 45, 46, 47, 48, 49, 50)}\) have shown no increased risk of tumor recurrence. Risk of second neoplasm in survivors of childhood cancer treated with GH analyzed in a report from the Childhood Cancer Survivor Study (CCSS) group, has revealed a small but significant increased risk of developing secondary neoplasm but the numbers are small and the elevation of risk due to GH use appears to diminish with increasing length of follow up.\(^{(51)}\) Therefore continuing surveillance is mandatory.\(^{(52, 53, 54, 55, 56, 57, 58, 59, 60)}\) A higher than expected incidence of and mortality from colonic cancer and Hodgkin’s disease has been reported in GH deficiency treated with hGH.\(^{(61)}\) However, the relatively small cohort and small number of cases argue for caution. Furthermore in the old days hGH was given twice or three times weekly which probably resulted in unphysiological high IGF-I levels. Available data in international databases do not support for excess malignancy in children treated with GH.\(^{(62)}\) There is no evidence of an increase in the incidence of \textit{de novo} intracranial tumours in childhood.\(^{(49)}\)

### Endocrine Problems

GH therapy does not cause a significant change in thyroid function. However, thyroid function should be evaluated prior to initiating therapy in GH deficiency.\(^{(53)}\) GH can modulate the activity of the enzyme 11\(\beta\)-hydroxysteroid dehydrogenase type 1 which is responsible for the conversion of cortisone to cortisol and prednisone to prednisolone. An increase in GH leads to a reduction in cortisol production.\(^{(64)}\) This interaction needs to be considered in patients receiving glucocorticoid replacement therapy.

### Other Undesirable Effects

Although \textit{in vitro} and \textit{in vivo} studies have shown that GH and IGF-I affect numerous immune functions,\(^{(65)}\) these abnormalities do not appear to be reflected in the clinical findings. Reports of anti GH antibodies in patients receiving GH have been few with
no adverse net result on growth response.

The potential adverse effect of GH on the number and size of nevi has been controversial but recent studies show no such effect.(66)

There is no increase in seizures on GH therapy.(2)

With respect to gonadal axis, there is no adverse affect on spermatogenesis, testicular volume and morphology in animal studies(67) and in databases of GH use in humans.(21) Gynecomastia has been reported as an adverse event with an incidence of 0.32/1000.(68) GH does not seem to have an effect on pubertal timing.(2) Although initial reports have stated that GH may accelerate bone age maturation,(69) this effect has remained as a controversial issue for years. However, it has been shown in some studies that when used in supraphysiological doses GH may accelerate bone age in idiopathic short stature (ISS). (70)

Acute pancreatitis is another possible rare complication of GH therapy.

**POTENTIAL ADVERSE EFFECTS IN SPECIFIC DIAGNOSTIC GROUPS**

There is no deterioration of renal function in patients with CRI on GH treatment.(71) An increase in the rate of graft rejection in GH treated children has been reported especially in those with a history of previous rejection episodes.(72) However, GH is used with success in children with CRI after renal transplantation. Careful monitoring of renal function is mandatory in patients after renal transplantation. Available data do not consistently show a significant risk for renal carcinoma in CRI after renal transplantation,(73) but in such patients routine ultrasound should be done to facilitate early tumor detection.

There is no increase in the frequency of otitis media in TS patients receiving GH.(74) Recent analysis of side effects in TS in a large pharmacoepidemiological survey(22) has revealed that it is very important to identify the risk factors in the natural history of the disease to be able to evaluate the potential adverse events. In this study, the incidence of certain events known to be associated with GH, including IIH, SCFE, scoliosis and pancreatitis, were increased compared to other non-TS cases in the survey. Type 1 diabetes was also increased. The aortic dissection/rupture incidence, the authors concluded, reflects the higher baseline risk for these events in TS. The ratio for de novo malignancies in the TS cohort seems to be increased compared to the rate in the general population although statistical significance was lacking.

The reported adverse events during GH treatment in patients with PWS are similar to those observed in other diagnostic groups. Low insulin levels prior to GH therapy increase during GH treatment. Glucose levels remain unchanged.(75) However, close follow up is mandatory.(76) Some children with PWS suffer from respiratory disturbances with chronic hypoventilation. There have been some reports of sudden death in patients with PWS upon GH therapy.(77) However the causality is still not clear. Furthermore GH therapy has a beneficial effect on ventilation and respiratory functions.(78, 79) However, prior to GH treatment patients with PWS should undergo polysomnography and tonsillectomy may be performed if needed. Children with upper respiratory tract infections should be monitored for sleep apnea.(79, 80)

In conclusion, the use of rhGH has a good safety record. However, some disorders that are already prone to certain complications such as TS, PWS and SGA should be carefully monitored for certain side effects.

**REFERENCES**


