Adverse effects of growth hormone replacement therapy in children

Efeitos adversos da reposição de hormônio do crescimento em crianças

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SUMMARY

Human growth hormone (hGH) replacement therapy has been widely available for clinical purposes for more than fifty years. Starting in 1958, hGH was obtained from cadaveric pituitaries, but in 1985 the association between hGH therapy and Creutzfeldt-Jakob disease was reported. In the same year, the use of recombinant hGH (rhGH) was approved. Side effects of rhGH replacement therapy in children and adolescents include rash and pain at injection site, transient fever, prepubertal gynecomastia, arthralgia, edema, benign intracranial hypertension, insulin resistance, progression of scoliosis, and slipped capital femoral epiphysis. Since GH stimulates cell multiplication, development of neoplasms is a concern. We will review the side effects reported in all rhGH indications. Arq Bras Endocrinol Metab. 2011;55(8):559-65

Keywords

Growth hormone; side effects; gynecomastia; intracranial hypertension; scoliosis; pediatrics; short stature

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SUMÁRIO

A terapia de reposição de hormônio de crescimento (hGH) tem sido amplamente disponível para uso clínico por mais de 50 anos. Inicialmente, em 1958, hGH era obtido de hipófises de cadáveres, mas em 1985 foi relatada a associação entre terapia com hGH e doença de Creutzfeldt-Jakob. No mesmo ano o uso de hGH recombinante (rhGH) foi aprovado. Os efeitos adversos que crianças e adolescentes em terapia de reposição de rhGH podem apresentar incluem erupção cutânea e dor no local da aplicação, febre transitória, ginecomastia pré-puberal, artralgia, edema, hipertensão intracraniana benigna, resistência insulínica, progressão de escoliose e epifisiólise da cabeça do fêmur. Como o GH estimula a multiplicação celular, o desenvolvimento de neoplasias é uma preocupação. Neste artigo, revisaremos os possíveis efeitos adversos do rhGH em cada uma de suas indicações clínicas. Arq Bras Endocrinol Metab. 2011;55(8):559-65

Descritores

Hormônio do crescimento; efeitos adversos; ginecomastia; hipertensão intracraniana; escoliose; pediatria; baixa estatura

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INTRODUCTION

Human growth hormone (hGH) has been used in GH deficient (GHD) children, adolescents and adults since 1958. The year of 1985 witnessed a switch from cadaveric pituitaries to recombinant hGH (rhGH) obtained from DNA-recombinant techniques, after the reports of Creutzfeldt-Jakob disease in hGH recipients (1). There has never been a case report of Creutzfeldt-Jakob with the use of rhGH.

The first rhGH was approved in 1985. Since then, prescription has been approved not only for GHD but also to a series of non-GH deficient patients, such as chronic renal failure, Turner syndrome, children born small-for-gestational age without height catch-up, Prader-Willi syndrome, idiopathic short stature, SHOX gene haploinsufficiency and Noonan syndrome (2).

In this report, we will review the side effects of the different therapeutic indications of rhGH.

Growth hormone deficiency

Glucose metabolism

GH physiologically antagonizes insulin effects in glucose and lipid metabolism by stimulating glycogenolysis and lipolysis, and inhibiting glycogenesis and lipogenesis. GHD is expected to increase insulin sensitivity, which can be clinically observed in GHD neonates with severe and persistent hypoglycemia at birth (3). Thus, treatment with rhGH is assumed to induce insulin resistance. This GH effect is observable, as type 2 *diabetes mellitus* (T2DM) is a classical feature in the context of excess GH in acromegaly (4). Nonetheless, there might be some increase in fasting and postprandial glucose and in plasma insulin during rhGH therapy, and the elevation may not be enough to overcome the threshold of glucose intolerance or T2DM in children who are not otherwise predisposed (5,6). The incidence and age at diagnosis of type 1 *diabetes mellitus* during rhGH treatment is similar to the general population (7).

Gynecomastia

Prepubertal gynecomastia is a rare and self-limited adverse effect of children in use of rhGH (8,9). It is characterized by the appearance of a breast bud in a prepubertal male, equivalent to the Tanner-stage 2 in normal female pubertal development. Reviewing "adverse drug experience" reports to United States Food and Drugs Administration (FDA) and data from pharmaceutical companies, Malozowski and Stadel reported 22 cases of prepubertal gynecomastia between ages of 2 and 12. The time from the initiation of therapy to the diagnosis of gynecomastia was found to be broad, varying between 0.5 month to 8 years. Since there was no data available on the number of children that have been exposed to rhGH in the populations from where the reports came, the incidence could not be estimated (9). Resolution occurred in two children after discontinuation of rhGH, and in five children still in use of the medication. Data was missing from the other cases (9). In general, there is no need for alteration in rhGH dosage, or discontinuation of medication, since gynecomastia is usually self-limited and will resolve with time.

Slipped capital femoral epiphysis

Slipped capital femoral epiphysis (SCFE) is defined as a posterior and inferior displacement of the proximal femoral epiphysis on the femoral neck (10). It occurs more frequently in periods of rapid height gain. Children with GHD are more prone to the development of SCFE, and rhGH replacement therapy may increase that risk by sevenfold. In a recent Kabi International Growth Study (KIGS) report, 52 from 57,968 children in rhGH therapy presented SCFE, in a total incidence of 73.4 per 100,000 patients year (11), while in the general population prevalence is 10.8 cases per 100,000 (12). Clinical suspicion should be considered in children complaining of unilateral or bilateral pain in the hips or knees. Treatment is always surgical, and involves in-situ screw fixation (12).

The measurement of the diaphyseal-epiphyseal angle (Southwick's angle), using anteroposterior pelvic radiography, at the beginning of therapy and annually thereafter, may be useful to assess individual risk. During normal growth spurt, Southwick's angle is expected to decrease with time, whereas it is significantly increased during rhGH treatment, leaving the patients at risk of epiphysiolysis (13).

Benign intracranial hypertension

Benign intracranial hypertension (BIH) or pseudotumor cerebri is the result of the physiological antidiuretic effect of hGH and is more evident in patients that cannot support a decrease in glomerular filtration rate. Normal children exhibit a mild transitory elevation in plasma renin activity and aldosterone, and rarely develop BIH unless other predisposing factors are present. Pseudotumor cerebri can be clinically suspected in children complaining of headaches, nausea, vomiting and presenting papilledema at fundoscopic examination. Cautioun should be taken so as not to misdiagnose papilledema in children with septo-optic dysplasia and optic disc hypoplasia, which are congenital defects and strengthen the diagnosis of GHD (14).

In patients with signs compatible with pseudotumor cerebri, clinical or imaging examinations should be performed. If the diagnosis of pseudotumor cerebri is confirmed, rhGH should be discontinued temporarily, and reinitiated later on, at lower doses.

Malignancies

As both GH and insulin-like growth fator-1 (IGF-1) have mitogenic and anti-apoptotic properties, there has always been a concern that rhGH might induce tumorigenesis. There are three issues involved in the relationship between GH and neoplastic induction: 1)

recurrence of a previously treated tumor; 2) induction of a second neoplasm; 3) appearance of a *de novo* malignancy.

GHD is one of the most common endocrine after--effects in the treatment of several malignancies. Surgical approach to intracranial tumors may affect the hypothalamus-pituitary axis, and therefore induce GHD, as well as cranial and whole-body radiotherapy for brain and neck tumors and leukemia.

The report of twelve cases of hematologic malignancy in a Japanese cohort on rhGH therapy raised concern on the safety of the medication (15). Eight of the patients had idiopathic GHD, and therefore leukemia would be a *de novo* malignancy; three had GHD secondary to cancer treatment; and one had Fanconi's anemia, which is a condition intrinsically associated with high incidence of leukemia (16). Despite the high risk of leukemia observed in the Japanese study, these results could not be replicated by other cohorts. The current position on the subject states that rates of new leukemia in non-Japanese patients without any known risk factors, and on rhGH replacement therapy are no greater than the expected ones for the general population (17).

The Childhood Cancer Survival Study (CCSS) follows up 13,539 survivors of childhood cancer. In the cohort of 361 patients treated with rhGH, the relative risk of developing a second neoplasm, mostly meningioma, was 3.21 (95% confidence interval, 1.88-5.46) (18). Additional 32 months of follow-up of the same cohort brought the relative risk down to 2.15 (95% CI, 1.33-3.47), still significant (19). Attenuation of relative risk over time may indicate that rhGH therapy anticipates the occurrence of a second neoplasm, which cancer survivors are already at risk. This speculation might be confirmed if further updates of the cohort with longer follow-up show progressive decrease in the relative risk. Cranial irradiation itself increases the risk of a second neoplasm, especially meningioma (20). Indeed, Mackenzie and cols. did not find significant difference in the incidence of a second neoplasm between rhGH--treated and untreated patients submitted to cranial radiotherapy (21).

Hence, in relation to the three issues, current data suggests that the use of rhGH does not increase the risk of development of malignancy, although it is still unclear whether the incidence of meningiomas might be increased in patients with GHD secondary to cranial irradiation. Yet, since in the normal population higher serum levels of IGF-I have been epidemiologically associated with increased risk of malignancy (22), monitoring is imperative, so that IGF-1 serum levels do not exceed the normal range for sex and age.

Long-term mortality

In December 2010 the French drug agency (AFSSAPS) and the European Medicines Agency (EMA) were informed of preliminary data of the SAGhE (Santé Adulte GH Enfant) study. SAGhE is a multinational European epidemiological study designed with the purpose to establish the long-term mortality rate in young adults who, during infancy and adolescence, initiated rhGH treatment between January 1985 and April 1997. France was the first country to start the study and was later followed by other European countries. Of the 6,928 French patients considered at low risk for mortality (isolated idiopathic growth hormone deficiency, short stature in children born small for gestational age, and idiopathic short stature), 93 patients died of all causes, an increment of nearly 30% when compared with the expected mortality of 70 persons based in a French population of reference. Cancer-related mortality was not increased. Even though malignant neoplasm of bone and joint cartilage had an expected mortality of 0.6, three patients who had received rhGH died. The expected mortality due to cardiomyopathy and cardiomegaly was of 0.28, and two patients died. The expected mortality due to non-traumatic intracranial hemorrhages was of 0.6, and four patients died (23,24). The use of rhGH doses above 50 mcg/kg/day was associated with the highest mortality rate.

The investigators concluded that these preliminary data should be analyzed with caution due to the low event rate, limited power, and potentially undetected confounders. Another important aspect is that SAGhE preliminary data from Sweden, Belgium and the Netherlands, presented at the 50th European Society of Pediatric Endocrinology Annual Meeting, in September 2011, showed that from a total of 2,858 low risk patients, there were no deaths due to cancer, bone or cerebrovascular disease.

Sharing SAGhE main investigators' perspective, a Drug Safety Announcement by the FDA and the EMA stated that no change in the prescription of rhGH should be made before SAGhE study is concluded and new long-term surveillance studies are conducted (25,26).

Chronic kidney disease

Children with chronic kidney disease (CKD) fail to grow within the parental percentiles for multiple reasons, related and unrelated to the GH-IGF-1 axis (27,28). The use of hGH in CKD growth disorder was approved by the FDA in 1993. Since then, it has been used in patients with predialytic CKD, in dialysis and after renal transplantation.

Before initiating rhGH therapy to CKD patients, it is imperative to improve nutritional status and to control metabolic acidosis, phosphorus and parathyroid hormone, so as to maximize GH actions on linear growth and to avoid the worsening of secondary hyperparathyroidism and the consequent development of bone deformities. Thus, phosphorus level should not be 1.5 times greater than the upper limit of normality (29).

Children with CKD-associated short stature in use of rhGH are more likely to develop BIH than those with other primary diseases (30), but not more likely than CKD patients without rhGH (31). Fine and cols. found no significant differences in the incidence of avascular necrosis, SCFE or any other serious adverse events, either (31).

As for the specific issues of CKD patients, the relationship between rhGH therapy and renal function has been thoroughly evaluated. Several studies show no effect on progression of kidney disease, deterioration of renal function or development of acute graft rejection (32-34).

Turner syndrome and SHOX gene haploinsufficiency

Turner syndrome (TS) is characterized by short stature, typical somatic features and delayed or absent spontaneous pubertal onset, with ovarian dysgenesis and consequent hypergonadotrophic hypogonadism. TS is caused by the complete or partial absence of the second X chromosome. Short stature homeobox (SHOX) gene is located in the pseudoautosomal region of both chromosomes X and Y. SHOX haploinsufficiency is believed to be the cause of short stature in TS, as well as in Leri-Weil dyschondrosteosis (OMIM #127300), and Langer mesomelic dysplasia (OMIM #249700).

Orthopedic outcomes

Children with TS should undergo orthopedic evaluation before initiating rhGH therapy. Scoliosis is one of the major concerns. From 49 TS girls followed by Ricotti and cols., 29 exhibited scoliosis at baseline, and other 9 developed minor new scoliosis during the 4-year follow-up (35). It appears that rhGH may be related to worsening of preexisting scoliosis. TS is also at increased risk of SCFE, and close monitoring should be performed for early detection of epiphysiolysis.

Nevi growth

Melanocytic nevi may be present as a feature of TS, and nevi count is greater in these patients than in both GHD children and control subjects before starting rhGH. Despite the fact that rhGH is able to activate melanocyte proliferation, studies showed no relationship between the number of nevi and the duration of rhGH treatment in any group (36,37). The incidence of skin cancer was not increased in TS children, either (38). These data demonstrates the benignity of melanocytic nevi in TS, and the absence of malignant transformation during rhGH therapy (38).

Overall mortality

Mortality in young TS girls is mostly due to congenital cardiac and aortic malformations, conditions that are unrelated to the use of rhGH. Neoplasms described in TS by Bolar and cols. are of different types and do not follow any specific pattern (39). The incidence of malignancies during rhGH treatment in this population did not reach statistical significance (39).

Children born small-for-gestational age

Ninety percent of children born small-for-gestational age (SGA) exhibit catch-up growth and reach familial height by the age of two (40). Some few children might undergo spontaneous catch-up growth between 2 and 4 years of age. The use of rhGH in SGA has been approved for children over 2 years-old by the FDA (41,42), and it was also approved by the Latin American consensus (43). Differently, the European Medicines Agency (EMA) determined that 4-year old was the age to start rhGH therapy for SGA without catch-up growth (44).

SGA condition implicates an intrinsic increased risk of cardiovascular disease and insulin resistance in adulthood. However, at the moment, there are no published data reporting increased risk of any specific side effect in this population. Since the dose of rhGH used in this condition is higher than in GHD, long-term safety data is needed.

Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a genetic condition derived from the lack of expression of the paternally imprinted chromosome 15q11-q13, and is characterized by hypotonia, short stature, hyperphagia, hypogonadism, scoliosis, psychomotor delay, and behavioral abnormalities (OMIM #176270).

Mortality rates in PWS are high when it is compared both with the general population and to people with intellectual disabilities from other causes (45). In infants and children, mortality is mainly due to sudden death and respiratory illness, and as they grow older, obesity and its complications, such as type 2 *diabetes mellitus*, hypertension, sleep apnea and cardiovascular disease, account for most of the deaths.

Since early 2000s, several cases of sudden death with a possible link to rhGH treatment have been reported (46). Further analysis did not show convincing data relating rhGH and mortality in this population. Since respiratory impairment is always a concern in PWS, it is advisable that, before initiating rhGH therapy, patients undergo a polysomnographic study. Nevertheless, there is no evidence linking the use of rhGH and respiratory morbidity in PWS (47).

Treatment with rhGH increases lean mass, decreases fat mass and improves the metabolic pattern of body fat distribution. In a long-term rhGH treatment study, there were no adverse effects in glucose homeostasis, blood pressure and lipid profile, and so it has been shown an effective and safe therapy for PWS patients (48).

Scoliosis is a common feature in PWS. Nakamura and cols. stated the prevalence at 38.6% (39 in a group of 101 patients) (49). Therapy with rhGH was found to induce neither the appearance nor the progression of scoliosis, affecting treated and untreated patients at equal rates (48.8% *vs.* 41.9%, p = 0.56) (50). The incidence of SCFE is low in PWS both children with and without rhGH therapy (11,51), even though obesity is closely related to the development of epiphysiolysis (52,53).

Idiopathic short stature (ISS)

Idiopathic short stature (ISS) is a diagnosis of exclusion of children with height below -2SDS, and no clinical and laboratorial signs of underlying disease. Because there are many subgroups within this diagnosis, such as familial short stature and constitutional delay of growth and puberty, studies show quite heterogeneous response to hGH therapy (54).

A report by the NCGS cohort of 8,018 patients, with a total exposure to rhGH of 24,817 patient-years, found no serious side effects specific to patients with ISS (55). Even so, due to the heterogeneity of this condition and the occasional use of higher doses, long-term follow-up is necessary.

Noonan syndrome

The latest indication of hGH therapy approved so far by FDA was Noonan syndrome, clinically presented with short stature, typical facial features, and congenital heart defects. In most patients, NS is characterized by mutations on PTPN11 gene (OMIM #163950). Although these mutations are closely related to the development of hematologic malignancies (56,57), rhGH does not seem to add to its risk. Cardiac malformations are a common feature in the clinical findings of Noonan syndrome. Yet, there are no reports of adverse cardiovascular events of rhGH therapy in this population (58). The incidence of side effects is no different from the expected one among GHD patients.

In conclusion, treatment with rhGH has been approved for GHD and a number of other non-GH deficient patients with growth impairment. In each one, it has been shown that rhGH therapy is efficient in increasing growth velocity and final height. Mild side effects are not unusual, although they are frequently transient and tolerable. In contrast, serious adverse events that require discontinuation of the medication are rare, but need to be continuously monitored throughout the treatment. Further epidemiological studies are required to establish the long-term safety of rhGH therapy in adults who were on treatment during childhood.

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