Case Report

ACROMEGALY AS A COMPLICATION OF GROWTH HORMONE THERAPY

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ABSTRACT

Objective: Growth hormone (GH) replacement is widely used; however, acromegaly as a complication of overreplacement is rarely reported. This case report explores this complication with the use of weight-based dosing regimens of human GH.

Methods: We report progressive features of acromegaly as a consequence of inadvertent overreplacement of GH, initiated for treatment of GH deficiency in an 11-year-old male treated for craniopharyngioma.

Results: An 11-year-old male developed panhypopituitarism after transsphenoidal resection of a craniopharyngioma. Human GH (hGH) replacement therapy was subsequently initiated for hypopituitarism, using a weight-based dosing regimen, achieving adequate linear growth. After 9 years of hGH replacement therapy, prognathism and an increase in shoe size were noted, with supporting radiographic evidence of hGH overreplacement.

Conclusion: Clinical features of acromegaly can develop as a rare adverse effect of overreplacement of hGH in GH-deficient patients treated with GH. Frequent clinical monitoring with appropriate GH titration should achieve target insulin-like growth factor 1 levels within the appropriate age- and sex-specific reference range. Awareness of the differences between adult and pediatric GH treatment dosing regimens is important as patients transition from childhood to adulthood. This case report provides valuable insight into this issue. **(AACE Clinical Case Rep. 2015;1:e68-e72)**

Abbreviations:
AACE = American Association of Clinical Endocrinologists; **GH** = growth hormone; **hGH** = human growth hormone; **IGF-1** = insulin-like growth factor 1

CASE REPORT

An 11-year-old male presented with persistent headaches and was diagnosed with craniopharyngioma in 1993. He subsequently underwent transsphenoidal surgery with an uneventful recovery. Six months postoperatively, a normal pituitary hormonal panel was indicative of intact pituitary hormone function. Bone age was in the low-normal range for chronologic age, although the patient manifested an attenuated growth velocity of 4 cm/year. In September 1994, insulin arginine growth hormone (GH) testing confirmed a normal GH response, with adequate insulin-like growth factor 1 (IGF-1) levels, despite delayed growth. Two years later, the patient complained of recurrent headaches and magnetic resonance imaging confirmed sellar tumor recurrence, requiring a second, more extensive transsphenoidal surgery in January 1996. Subsequent pituitary hormone evaluation revealed panhypopituitarism with central hypothyroidism and central adrenal insufficiency, necessitating replacement with levothyroxine and hydrocortisone. The patient also developed polyuria, polydipsia, and hypernatremia, consistent with diabetes insipidus, and treatment with Desmopressin nasal spray was initiated.

In May 1996, 4 months after the second surgery, when the patient was 14 years of age, persistent slowed growth was noted. Repeat bone age revealed a bone age 1 SD below chronologic age; his IGF-1 was 91 ng/mL (Tanner

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stage I-II normal IGF-1, 109 to 512 ng/mL). Subsequent IGF-1 levels 3 months later showed a further decline, with IGF-1 levels <15 ng/mL. Insulin arginine GH stimulation testing confirmed a decreased GH response. Human GH (hGH; Nutropin) replacement therapy was initiated (Fig. 1). The hormone was prescribed as a 10-mg vial to be diluted in 2.5 mL and injected as 0.5 mL nightly, for a total daily dose of 2 mg (i.e., the recommended starting dose of 40 μg/kg/day [the patient's weight at that time was 47.8 kg]). Bone age was reevaluated 4 months after treatment initiation, showing persistent low bone age 2 SD below chronologic age. IGF-1 level obtained 10 months after initiation of GH therapy was 529 ng/mL (normal, 174 to 512 ng/mL). Weight-based escalation in hGH dose was instituted, to 2.16 mg daily, as the patient's body weight had increased to 51.4 kg (Fig. 2). The patient, now 16 years old, experienced persistent fatigue. His testosterone level was noted to be low, and he was started on testosterone 200-mg injections intramuscularly every 3 weeks. Repeat bone age was 13 ± 0.5 years; his hGH dose was increased to 2.32 mg daily according to a weight increase to 53.5 kg; however, IGF-1 levels were not obtained at that time. Dose titration per body weight was continued. In January 2000, the patient was on 2.25 mg and had "excellent growth" (Fig. 3). From age 18 to 20 years, his hGH dose was gradually increased to 4 mg per day. Repeat testing at age 20 revealed bone age of 15.5 years, 2 SD below chronologic age, normal bone mineralization, with complete fusion of the distal epiphysial phalanges. In August 2003, an IGF-1 level was obtained, with a result of 879 ng/mL (normal, 127 to 424 ng/ml).

The same hGH dose was continued until March 2004, at which time the dose was decreased to 1.5 mg daily; however, due to misunderstanding, the patient continued the same dose of 4 mg for the following year. Repeat IGF-1 in October 2004 was 889 ng/mL (normal, 116 to 358 ng/mL), testing again in February 2005 revealed an IGF-1 level of 871 ng/mL. The hGH dose was finally reduced in February of 2005, when patient was 22 years of age, to the intended dose of 1.5 mg and further reduced in May of that year to 0.75 mg daily. In the interim, the patient noticed enlargement of his lower jaw. He also admitted to significant weight gain and increased shoe size.

After hGH dose reduction, IGF-1 levels returned to normal, but bony features suggestive of acromegaly have persisted, and the patient is awaiting surgical correction of prognathism and overbite.

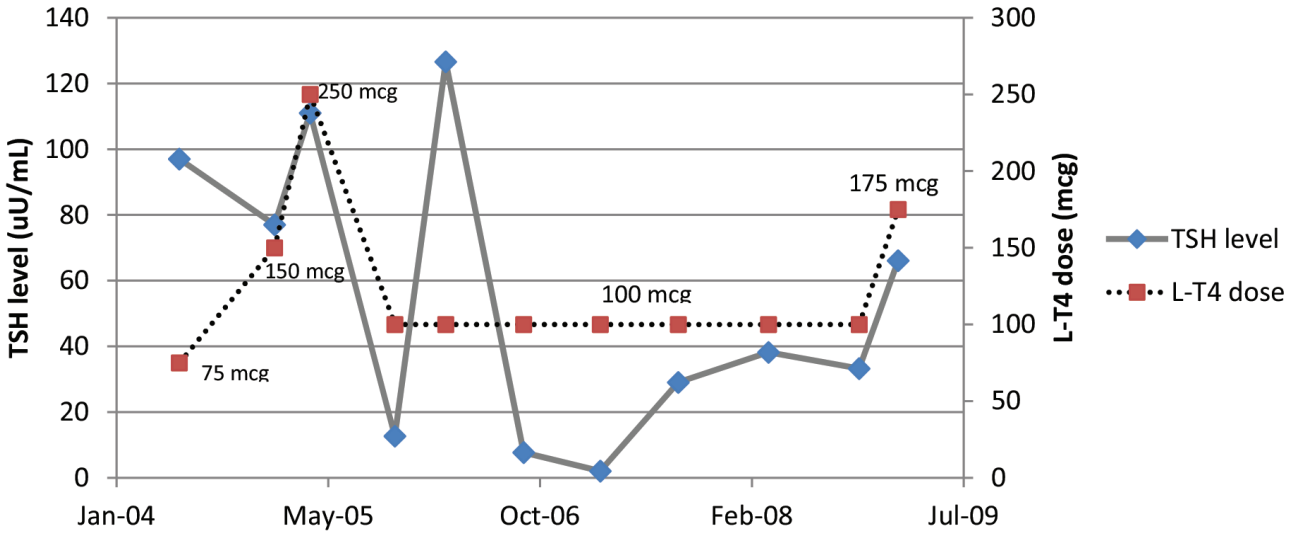

Fig. 1. Progression of patient's physical characteristics over time. Age in years is indicated below each year. Shown in green is the growth hormone dose (in mg) as it coincides with clinical picture over time.

Fig. 2. Human growth hormone (hGH) dose (in mg) and insulin-like growth factor 1 (IGF-1) serum level (in ng/mL) over time. Normal IGF-1 range is displayed in gray. Dotted red line indicates the time period in which IGF-1 levels were not obtained.

DISCUSSION

Several GH dosing regimens have been used in clinical practice, including fixed-dose, weight-based, and growth velocity–based. Historically, GH dosing in both the pediatric and adult population was weight-based, often resulting in supraphysiologic doses with a high side effect profile (1,2). IGF-1 levels are used for monitoring adequacy of GH replacement with all of the above regimens. Individualized GH dose adjustments based on the IGF-1 level continue to be studied to further optimize GH replacement therapy and outcomes (3). The American Association of Clinical Endocrinologists (AACE) defines GH deficiency in patients with irreversible hypothalamic-pituitary structural lesions and those with panhypopituitarism (at least 3 pituitary hormone deficiencies) as a serum IGF-1 levels below the age- and sex-appropriate reference range. Current AACE recommendations for GH-deficient adults and transition patients recommend that GH dosing regimens should be individualized independent of body weight (4). Although there is lack of consensus regarding the optimal approach to the GH dosing regimen, AACE and Endocrine Society guidelines both propose initiating GH therapy at a low dose, with gradual adjustment, until serum IGF-1 levels are normal, appropriate for age and sex, without causing unacceptable side effects (4,5). This case report supports the use of an individualized GH dosing regimen, with titration based on IGF-1 levels rather than a weight-based titration method, which was employed (6). Furthermore, diligent clinical monitoring of growth velocity and increase in height as well as regular evaluation of serum IGF-1 levels is mandatory to ensure appropriate growth rates and final height and to avoid side effects of GH overreplacement (7).

GH stimulates skeletal growth indirectly by stimulating hepatic IGF-1 production, which then stimulates bone

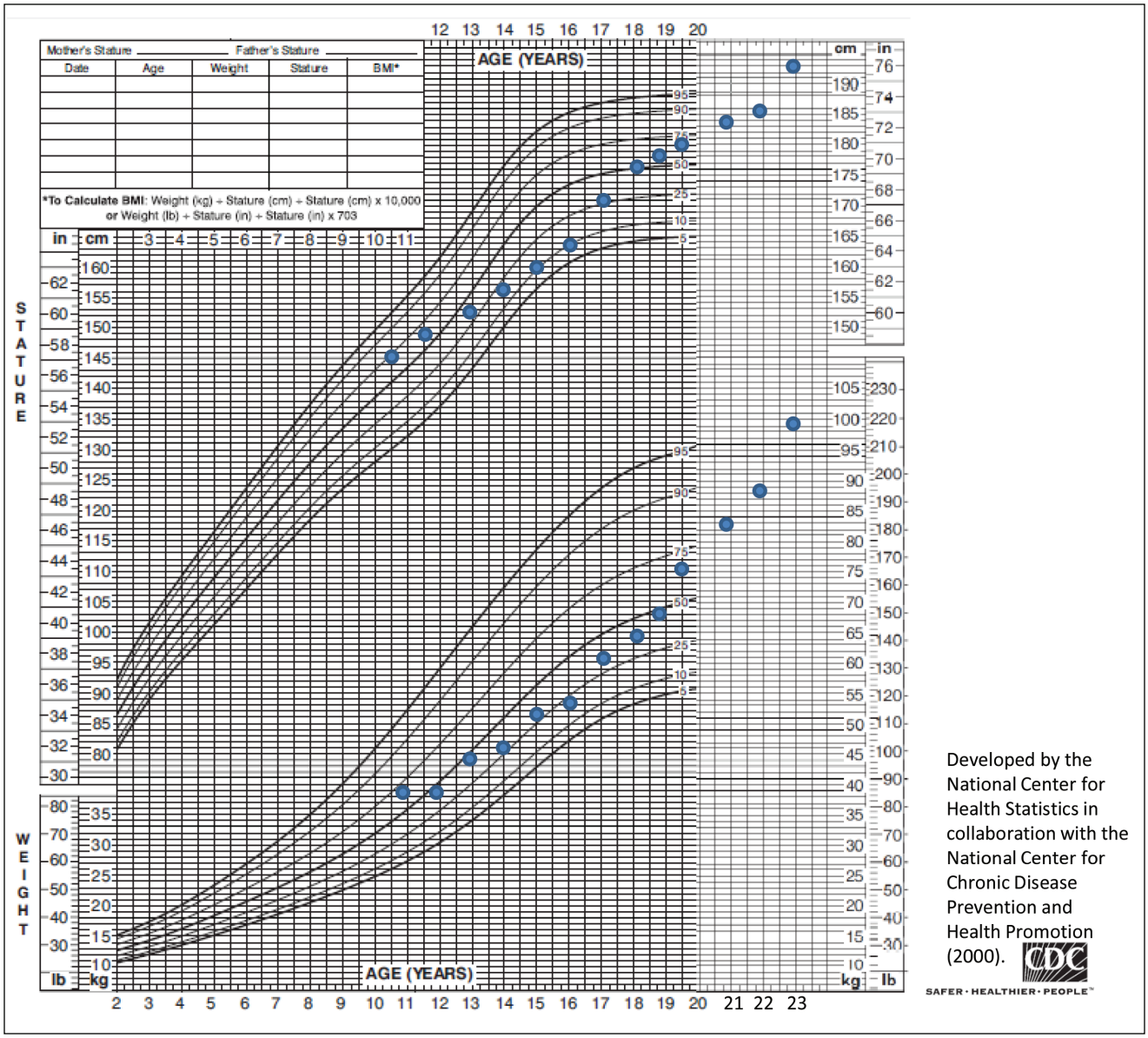

Fig. 3. Boys growth chart for ages 2 to 20 years, with stature-for-age (top) and weight-for-age (bottom) percentiles. The extension beyond 20 years was added to show progression of the patient's height and weight.

growth (8). Bone growth is characterized by bone modeling, which, unlike bone remodeling, is a process of uncoupled bone formation and bone resorption (9). GH and IGF-1 exert their anabolic effects by periosteal bone apposition, a process of matrix deposition at the outer surface of bone, which results in increased bone width and skeletal strength (9). These bony changes may explain the characteristic bone deformities seen in acromegaly with excess endogenous GH (9), or as in this case, excess exogenous GH.

CONCLUSION

Two case reports have described complications of acromegaly as a side effect of hGH replacement therapy (10,11). We report a further case of acromegaly comorbidities caused by hGH overreplacement, presenting as prognathism with an overbite and increase in shoe size.

DISCLOSURE

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