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BRIEF REPORT

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Hyperparathyroidism during growth hormone treatment: a role for puberty?

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Abstract We describe three adolescent patients on chronic hemodialysis with a pubertal growth spurt who developed severe hyperparathyroidism during recombinant human growth hormone treatment. Parathyroid hormone levels were raised in parallel with the increase in linear growth in all patients. In two patients, hyperparathyroidism was successfully controlled with an increase in calcitriol dosage. In the third patient, growth hormone had to be withdrawn. We discuss the possibility that puberty is a risk factor for the development of hyperparathyroidism during growth hormone therapy.

Key words Hyperparathyroidism · Growth hormone · Hemodialysis · Puberty

Introduction

Growth hormone induces acceleration of bone turnover, osteoblast proliferation, and formation of new bone [1]. Sporadic cases of severe hyperparathyroidism (HPT) have been described during recombinant human growth hormone (rhGH) treatment of uremic children [2–7]. The pathophysiological reasons for this complication are poorly understood. In some patients, HPT was associated with a poor response to rhGH [2] or with acquired orthopedic abnormalities, such as femoral avascular necrosis and slipped capital femoral epiphysis [7]. In other reports, however, good statural growth has been reported, despite development of renal osteodystrophy [4–6]. We report here three male adolescent patients treated with rhGH in whom a major increase in parathyroid hormone (PTH) levels, peak height velocity (HV), and pubertal spurt coincided.

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Case reports

Patient 1 developed chronic renal failure (CRF) secondary to focal and segmental glomerulosclerosis and was started on chronic hemodialysis (HD) at the age of 11.4 years. He underwent a cadaver kidney transplantation at 14.2 years of age, but rapidly lost his graft because of recurrence of his primary renal disease. He re-entered an HD program after 6 months. rhGH was started for severe growth retardation [height 138 cm, height standard deviation score (HSDS) –4.8, HV 0.3 cm/year] at 15.2 years of age. Bone age was 11.5 years (TW2). At that time, the patient was pubertal stage P2G1 and plasma testosterone levels were undetectable. On discontinuation of HD, he received calcium carbonate ($CaCO_{3)}$ (0.05–0.15 g/kg per day) and oral calcitriol (CT) (7 ng/kg per day). PTH levels were between 46 and 120 pg/ml. During rhGH treatment, serum Ca levels remained within normal limits, with relatively stable phosphate levels (Fig. 1). After 18 months of therapy, PTH levels began to rise, and CT and $CaCO_3$ dosages were increased from 7 to 44 ng/kg per day and from 0.15 to 0.36 g/kg per day, respectively. At that time, the patient was pubertal stage P3G3 and plasma testosterone levels were 389 ng/dl. PTH levels, however, increased, reaching 1,037 pg/ml after 24 months of treatment when the HV was 6.7 cm/year. Hand X-rays showed mild signs of osteodystrophy. Subsequently, PTH levels decreased and rhGH was continued until complete calcification of cartilaginous growth plates.

Patient 2 had been on HD since the age of 11.9 years, because of CRF secondary to polycystic kidney disease. At 12.8 years of age, the patient's height was 143.3 cm (HSDS –2.4, HV 1.1 cm/year). Bone age was 12.0 years. rhGH was started. Pubertal stage was P2G1 and plasma testosterone levels were undetectable. During the first 6 months of rhGH treatment, he was treated with oral CT (7 ng/kg per day) and $CaCO_3$ (0.01–0.12 g/kg per day) and had normal PTH serum levels (24–83 pg/ml). HV and PTH increased and reached a peak value of 6.0 cm/year and 1,295 pg/ml after 12 and 18 months of rhGH treatment, respectively (Fig. 1). After 15 months of treatment, CT and $CaCO_3$ dosages were increased to 44 ng/kg per day and to 0.36 g/kg per day, respectively. After 20 months of rhGH treatment, mild signs of radiological osteodystrophy appeared. After 24 months of rhGH, the patient became pubertal stage P3G3 and plasma testosterone levels were 151 ng/dl. PTH levels decreased to 87 pg/ml in the ensuing 9 months, allowing continuation of rhGH until completion of puberty.

Patient 3 started chronic HD at 11.1 years of age because of CRF secondary to nephronophthisis. This patient underwent a ca-

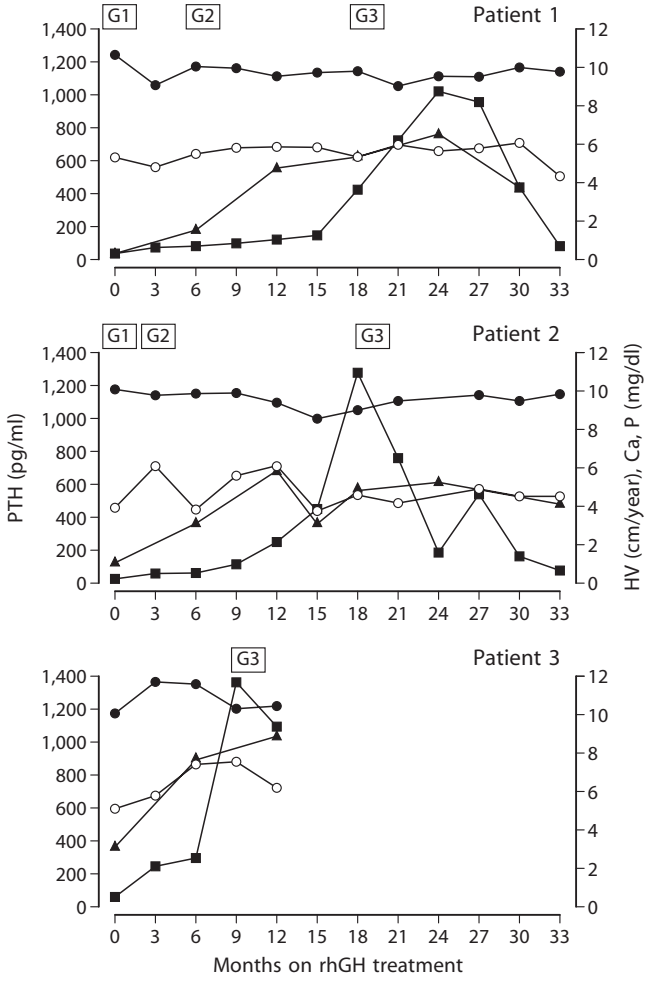

Fig. 1 Parathyroid hormone (*PTH*) (■), calcium (*Ca*) (●), phosphate (*P*) (○), height velocity (*HV*) (◆), and genitalia pubertal stage (*G*) (in *squares*) in three pubertal children during recombinant growth hormone (*rhGH*) treatment

daver donor transplantation at 12.1 years of age, but lost his graft during the 1st post-transplant week because of renal artery thrombosis. rhGH was initiated at 12.3 years of age when the patient measured 146 cm (HSDS –0.3, HV 3 cm/year) and was pubertal stage P3G3. Bone age was 12.0 years. At that time, the patient was receiving CT (11 ng/kg per day), was not taking $CaCO_3$, and had normal PTH levels (24–60 pg/ml). After starting rhGH, PTH levels increased rapidly (Fig. 1). Oral CT treatment was changed from 21 ng/kg per day to three pulses/week of 74 ng/kg each, and $CaCO_3$ dosage was increased from 0.10 to 0.32 g/kg per day. After 9 months of treatment, PTH levels reached 1,377 pg/ml and HV 9 cm/year. At that time, the patient was P4G3 and testosterone plasma levels were 402 ng/dl. rhGH was stopped because of arterial hypertension and severe radiological signs of osteodystrophy. Three months after rhGH withdrawal, PTH levels decreased and arterial blood pressure was back to normal values.

All three patients were treated with 0.75–1.0 IU/kg per week of rhGH. No patient had acidosis, severe anemia, or an inadequate nutritional intake. Ultrasonography of the parathyroid glands did not reveal evidence of adenoma. Alkaline phosphatase paralleled PTH levels. The dialysate calcium concentration was 3.5 mEq/l in all cases. No bone biopsy was performed.

Discussion

The three patients presented developed a steep increase in intact PTH after rhGH treatment during their pubertal spurt. To our knowledge, the association of pubertal stage and HPT during rhGH treatment has never been examined. In the published reports of HPT during rhGH treatment, both children and adolescents are described. Fujisawa and Kida [3] described a 14-year-old girl with CRF and Kaufman [6] described a 14.5-year-old boy on chronic HD; both developed severe HPT. Sieniawska et al. [4] studied 26 children aged 5–15 years on chronic dialysis and reported the highest PTH levels (3,500 pg/ml) in a 14-year-old boy. In the reports of Langman et al. [2] and Bérard et al. [8], the age of patients who developed HPT is not specified. We previously reported higher PTH levels in 11 children on HD treated with rhGH during the pubertal growth spurt, compared with those observed in the prepubertal stage [5].

Two possible mechanisms may explain HPT during rhGH treatment: a direct effect of rhGH on parathyroid glands or PTH hypersecretion secondary to rapid bone remodelling. A direct effect of growth hormone on PTH secretion has been hypothesized in animals [9], but seems unlikely in humans: PTH levels do not vary in patients with hypopituitarism treated with rhGH [10, 11].

Increased PTH activity secondary to increased bone metabolism has been hypothesized [8] in children on HD receiving rhGH. In adult uremic patients, however, rhGH did not induce any significant change of PTH levels [12]. Moreover, children with isolated GH deficiency treated with significantly lower dosages of rhGH than those used in uremic children (0.6 vs. 1.0 IU/kg per week) showed mean PTH levels slightly exceeding the upper normal limits after 12 months of treatment [13]. Thus, three conditions are probably necessary for the establishment of HPT following rhGH treatment: (1) a growing skeleton, (2) a tendency for HPT, as in chronic uremia, and (3) a high rhGH dosage.

In normal subjects, maximal bone growth is induced by the synergistic actions of endogenous GH, insulin-like growth factor-1, and sex steroid hormones during puberty [14]. However, PTH levels are not increased during puberty [15, 16]. In uremic children and adolescents, rhGH treatment induces increased bone turnover [4], and the pubertal growth spurt occurs in almost all individuals, although often after a considerable delay [17, 18]. There are no reports demonstrating a possible influence of puberty on PTH levels in uremic patients. Behnke et al., however, reported that adolescents with CRF have the highest levels of bone alkaline phosphatase during pubertal stage III and that these levels correlate significantly with PTH [19]. It is interesting to note that in all our patients PTH levels exceeded 200 pg/ml when the pubertal stage was between G2 and G3 (Fig. 1).

Although interpretation of the clinical evolution is limited by the absence of bone biopsy, the combined elevation of PTH and alkaline phosphatase levels with radiological features of osteodystrophy make a high turn-

over bone disease very likely. It is tempting to speculate that abnormal PTH secretion is triggered by the combined action of elevated dosages of rhGH and puberty in uremic patients with underlying or latent HPT.

Whether HPT during rhGH treatment is mediated by phosphate and/or ionized calcium changes, or by other unknown mechanisms, remains unclear. Kaufman [6] reported a decrease in total calcium levels to 8.5 mg/dl and a rise of serum phosphate to 7.6 mg/dl coinciding with PTH peak values in an adolescent on chronic HD with severe HPT during rhGH treatment. In our patients, phosphate levels remained relatively stable during rhGH treatment, ranging from 3.8 to 6.1 mg/dl in patients 1 and 2, and increasing from 5.1 to 7.8 mg/dl in patient 3. Calcium levels remained within normal limits. Only a very small decrease in serum calcium was observed before PTH reached peak values in patients 1 and 2. In patient 3, total calcium levels decreased from 11.5 to 10.4 mg/dl in parallel with PTH peak values (Fig. 1). Unfortunately, ionized calcium levels were not available. Therefore, we cannot exclude that a decrease in ionized calcium levels and/or a rise in serum phosphate could have triggered increased PTH secretion in these patients.

In summary, we report an association between the pubertal spurt and HPT in three adolescents on chronic HD during rhGH treatment. This association in a limited number of patients suggests a possible role of puberty in inducing or worsening HPT in patients with CRF. A larger cohort of patients is required to confirm these data. In the interim, we believe that particular attention should be paid to PTH levels during accelerated growth in adolescents with renal disease treated with rhGH. The possibility should be considered that puberty (i.e., period of maximal bone turnover) could be an additional risk factor for the development of HPT in these patients. Under these circumstances, sufficient calcium intake, strict phosphate control, and an increase in vitamin D dosage should be considered.

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