

Case Report

Failure of Growth Hormone Therapy in a Girl with Growth Hormone Deficiency and Steroid - induced Growth Failure Caused by Prednisolone Administration

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SUMMARY

We administered recombinant growth hormone (rGH) to a girl with systemic lupus erythematosus (SLE) complicated by steroid - induced growth failure and GH deficiency. However, the rGH therapy, which she underwent for 14 months, was not effective. The patient was diagnosed as SLE when she was 4 years and 10 months old, and her height before undergoing prednisolone was -1.0 SD score (SDS). She was treated with prednisolone (0.4 - 0.5 mg/kg/day) for a prolonged period. She was referred to us at 9 years of age because of persistent proteinuria that had begun when she was 7 years and 8 months old. We performed a renal biopsy (WHO SLE IIIA type) and noticed steroid - induced growth failure (-4.2 SDS), delay of bone maturation (5 years of age) and a low response to GH in the arginine and clonidine - loading test. We prescribed rGH therapy (0.175 mg/kg/week) and attempted to decrease prednisolone by administering cyclosporin A or mizolibine. However, prednisolone could not be decreased to less than 0.35 mg/kg/day for a long period. GH therapy for 14 months increased her height by only 2.8 cm (-4.4 SDS). The observations made in this SLE patient are consistent with those of Rivkees et al., who reported that when the prednisolone dose is greater than 0.35 mg/kg/day, rGH therapy does not increase the linear growth rate.

Key Words : glucocorticoids, growth hormone deficiency, growth hormone therapy, lupus nephritis, short stature, steroid - induced growth failure

INTRODUCTION

Glucocorticoid (GC) therapy for a prolonged period can result in impaired linear growth. Rivkees et al.¹⁾ reported that when the prednisolone dose was greater than 0.35 mg/kg/day, recombinant growth hormone (rGH) therapy did not increase the linear growth rate in 7 children with asthma, renal transplant, or nephrotic syndrome (NS). However, Loke et al.²⁾ reported that one year of rGH therapy increased the height of 8 children with steroid - dependent NS requiring prednisolone

(mean dose 0.46 mg/kg/day) to maintain remission. In these reports^{1,2)}, none of the patients were reported to have an associated GH deficiency.

We report that rGH therapy had no effect in a girl with systemic lupus erythematosus (SLE) complicated by steroid - induced growth failure (prednisolone dose between 0.50 and 0.22 mg/kg/day) and GH deficiency.

CASE REPORT

The patient was diagnosed as SLE when she was 4 years and 10 months old by a dermatologist, based on the positive findings of a butterfly eruption on the face, photosensitivity, arthritis, leukopenia (WBC 3200/ μ l), positive anti - ssDNA antibody (76 AU/ml), positive antinuclear antibody (160 times), and low levels of serum CH50 (15 U/ml), C₃ (35 mg/dl) and C₄ (6 mg/dl).

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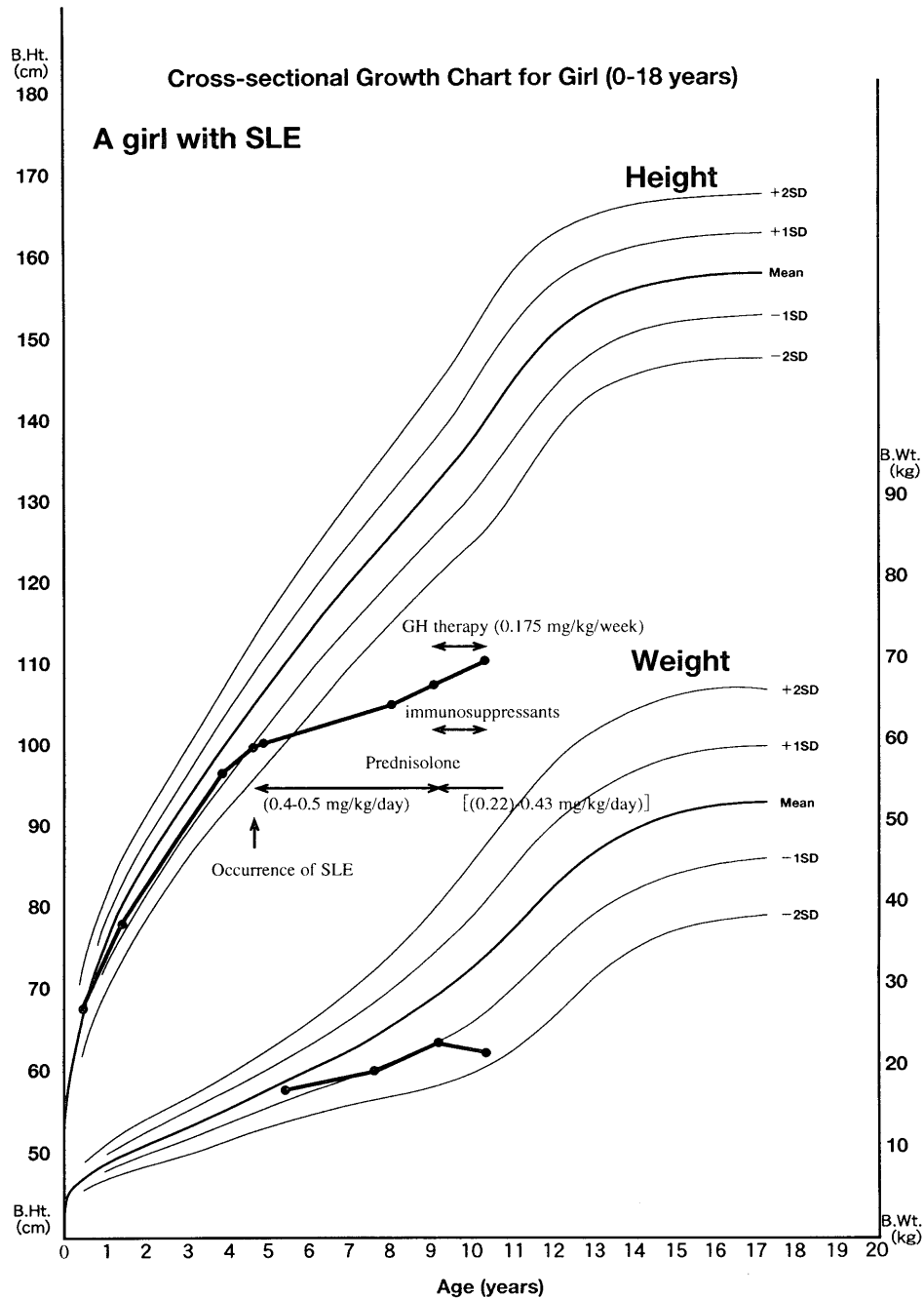


Fig. 1 Cross-sectional growth chart, and clinical and treatment course in a girl with systemic lupus erythematosus complicated by steroid-induced growth failure and growth hormone deficiency

Urinalysis was normal and her height before prednisolone therapy was -1.0 SD score (SDS). She was subsequently treated with prednisolone (0.4 – 0.5 mg/kg/day) and alfacalcidol. In spite of treatment, her serum complement level remained low, and her anti-ssDNA antibody and antinuclear antibody levels remained high. Proteinuria (2+; about 100 mg/dL) developed when she was 7 years and 8 months old. She was referred to us

at 9 years of age because this proteinuria persisted. We performed a renal biopsy (WHO SLE IIIA type) and noticed steroid-induced growth failure (Fig. 1), and a delay in bone maturation (5 years of age). Her height was 107.5 cm (-4.2 SDS), her weight was 23.0 kg (-1.0 SDS), and her secondary sexual characteristics were of Tanner stage I. Serum insulin-like growth factor I and insulin-like growth factor binding protein-3 were 179.6

ng/ml (sex- and age- matched normal value ; 170 – 962), 2.29 μ g/ml (age- matched normal value ; 2.33 – 4.91), respectively. The peak GH levels revealed by provocation testing with arginine and clonidine were 4.2 and 4.2 ng/ml, respectively. As this patient satisfied the criteria for GH deficiency, she was treated with 0.175 mg/kg/week recombinant GH (rGH) therapy from the age of 9 years and 2 months. We also attempted to decrease the prednisolone dose by administering cyclosporin A (2.2 mg/kg/day, trough levels ; 46 – 72 ng/ml) for 4 months. However, the dose of prednisolone could be decreased from 0.43 mg/kg/day to 0.22 mg/kg/day for only one month, because arthritis and high fever developed due to the decreased prednisolone dose. We subsequently increased the prednisolone dose again from 0.22 mg/kg/day to 0.43 mg/kg/day, and replaced cyclosporin A with mizoribine (50 mg/day) for 10 months. Her height after 14 months of rGH therapy was 110.3 cm (– 4.4 SDS) and her weight decreased to 22.6 kg (– 1.8 SDS). Urinary protein in the morning was 16 – 72 mg/dl during combination therapy with prednisolone and cyclosporine A, and was 17 – 96 mg/dl during combination therapy with prednisolone and mizoribine. Serum complement, anti-ssDNA antibody and anti-nuclear antibody levels were abnormal during these combination therapies with prednisolone and cyclosporin A or mizoribine.

DISCUSSION

The dose of rGH in GH deficient children in Japan is limited to 0.175 mg/kg/week. However, Rivkees et al.¹⁾ and Loke et al.²⁾ administered rGH for patients with steroid-induced growth failure at 0.30 mg/kg/week and 0.32 mg/kg/week (double the dose we administered to our patient), respectively. Rivkees et al.¹⁾ reported that there was no increase in the linear growth rate with rGH therapy when the prednisolone doses were greater than 0.35 mg/kg/day, as demonstrated in a study of a heterogeneous group of 7 patients with asthma (n = 2), NS (n = 1), and post renal transplantation (n = 4), who had a marked steroid-induced short stature (mean \pm SD ; -3.7 ± 1.0). Loke et al.²⁾ reported that the mean height (SDS) following rGH therapy increased from -1.4 ± 1.6 to -0.3 ± 1.1 in 8 children with steroid-dependent NS (mean prednisolone dose 0.46 mg/kg/day). Four of the patients studied by Loke et al. were receiving

less than 0.30 mg/kg/day of prednisolone. The difference between the studies of Rivkees et al. and Loke et al. was the height SDS before rGH therapy. The height SDS of our patient was similar to those of the study by Rivkees et al. Allen and Goldberg³⁾ reported that rGH therapy (0.30 mg/kg/week) was effective in 7 heterogeneous patients who were treated with prednisolone at a dose of less than 0.36 mg/kg/day, and were -2.4 ± 0.9 SDS in height before undergoing rGH therapy. Sano et al.⁴⁾ reported that the administration of 0.175 mg/kg/week of rGH was slightly effective in 3 nephrotic patients (-3.5 , -3.3 and -3.8 SDS in height after rGH therapy, respectively) treated with prednisolone (0.66, 0.56, and 0.78 mg/kg on alternate days, respectively) and with severe steroid-induced growth failure and GH deficiency (-3.5 , -4.1 and -4.3 SDS in height before rGH therapy, respectively). Sano et al.⁴⁾ reported that rGH therapy is effective in patients with GH deficiency. However, in our patient, whose SLE was complicated by GH deficiency, GH therapy was not effective. The differences between the patients reported by Sano et al. and our patient were that prednisolone was administered daily and on alternate days, respectively, and that the prednisolone dose was slightly higher in our patient. No report has clarified whether or not there is a difference in the efficacy of rGH therapy between patients with and without GH deficiency with steroid-induced growth failure.

All of these reports^{1~4)} studied a small number of patients. Recently, Allen et al.⁵⁾ reported on a large number of patients with steroid-induced growth failure (n = 83 ; 45 transplant, 18 inflammatory, 16 asthma and 4 others). The prednisolone equivalent dose and growth response to GH therapy was found to be negatively correlated ($r = -0.264$; $p < 0.05$). They also reported that there was no increase in the linear growth rate by rGH administration (0.29 mg/kg/week) in 4 of 41 patients (9.8%) when the prednisolone dose was less than 0.35 mg/kg/day, and that there was no increase in the linear growth rate by rGH administration in 9 of 42 patients (21.4%) when the prednisolone dose was more than 0.35 mg/kg/day. The pathogenesis of growth suppression by prednisolone is complex and multifactorial, involving several steps in the cascade of events that lead to linear growth. Glucocorticoids interfere with nitrogen and mineral retention, inhibit bone formation and chondrocyte mitosis, impair collagen synthesis and its degradation,

inhibit pulsatile GH release, reduce GH receptor expression and signal transduction, and inhibit the action of insulin-like growth factor I.⁵⁾ As it has been demonstrated that rGH therapy is more effective in the presence of low prednisolone doses^{1, 5)}, we attempted to decrease the prednisolone dose by administering cyclosporin A^{6, 7)} or mizoribine^{8, 9)}, both of which can provide effective treatment for SLE. Our attempts failed, because the doses of cyclosporin A (2.2 mg/kg/day) and mizoribine (50 mg/day) were low. In the future, we will attempt to decrease the prednisolone dose by administering an increased dose of cyclosporin A (3–5 mg/kg/day) or mizoribine (150 mg/day).

GH therapy may increase cytochrome P-450 antipyrine clearance in humans¹⁰⁾. Therefore, careful monitoring of cyclosporin A trough levels is advisable when rGH is administered with an increased dose of cyclosporin A. Cyclosporin A is metabolized by cytochrome P-450¹¹⁾, and an increase in the cyclosporin A dose may be required in patients undergoing rGH therapy.

In conclusion, the effect of rGH therapy in patients with marked steroid-induced growth failure and GH deficiency is influenced by the dose of prednisolone.

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