

## Case Reports

# Growth hormone deficiency in autoimmune polyglandular disease type 1

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### ABSTRACT

This is a case report of 2 patients who were diagnosed to have autoimmune polyglandular disease type 1. Both developed mucocutaneous candidiasis, hypoparathyroidism, vitiligo, and adrenocortical insufficiency. Both were noticed to have subnormal linear growth velocity and delayed bone age. Both showed subnormal stimulated serum growth hormone values indicating growth hormone deficiency. The first case showed favorable response to growth hormone therapy.

**Keywords:** Autoimmune polyglandular, growth hormone deficiency.

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Autoimmune polyglandular disease type 1 described first by Thorpe and Handley in 1929 and further defined by Gas in 1962, is a disease characterized by mucocutaneous candidiasis and multiple organ involvement which prominently aggregates in sibships predominantly young females.<sup>1,2</sup> Affected organs may include the parathyroid, the adrenal cortex, gonads, pancreatic B cells, gastric parietal cells and the thyroid.<sup>3,4</sup> Hepatitis, alopecia, vitiligo and keratopathy may also be associated.<sup>3,5</sup> Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), multiple endocrine deficiency-autoimmune candidiasis (MEDAC), and autoimmune polyendocrinopathy candidiasis syndrome (APECS) are frequently used terms to describe this condition.<sup>3,5,6</sup> Short stature may be a complication of this condition due to many contributing factors. However, growth hormone deficiency has not been reported as a contributing factor to short stature. We describe a girl and a boy who have this condition who were also found to be growth hormone deficient.

### Case Report

**Patient 1.** A 17-year-old caucasian girl was troubled with oral thrush after birth which followed normal pregnancy and delivery. Severe photophobia and ptosis due to severe keratitis and conjunctivitis was established at 4 years of age. At 4½ years of age, she presented with parasthesia of her hands and feet which was subsequently found to be due to hypocalcemia caused by hypoparathyroidism evidenced by a calcium level of 1.75 mmol/L, phosphate of 2.73 mmol/L and simultaneous parathyroid hormone of less than 2.1 pmol/L (normal: 10-65). The latter was repeated on 3 subsequent occasions and remained low at 1, 4 and 3 pmol/L. Total protein, albumin and magnesium were 71 g/L, 38 g/L and 0.85 mmol/L. Her hypoparathyroidism was treated with 1,25 dihydroxyvitamin D<sub>3</sub>. Vitiligo involving her face, trunks and hands, and alopecia developed at 11 years of age. Nails dystrophic deformity involved mostly the left thumb but also intermittently the 2nd and 3rd

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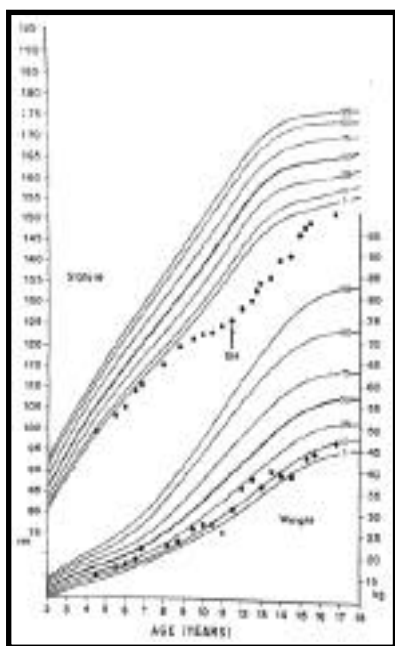


Figure 1 - The growth chart of patient number 1.

fingers and toes. She was treated with ketoconazole, clotrimazole and gentian violet. Her hemoglobin was 10.2 g/dl and she was therefore treated with iron. Serum folate and vitamin B12 levels were normal at 20.0 mmol/L and 163 pmol/L. Thyroid stimulating hormone (TSH) was 1.3 U/L, and thyroxine (T4) was 101 nmol/L. Her nutrition was adequately reflected on normal weight gain till the age of 10 years when she started to experience increasing fatigability, hyperpigmentation and weight loss. Stimulation with 250 ug of intravenous aqueous ACTH showed cortisol levels of less than 25 nmol/L at 0, 40, 60, 90, and 120 minutes. Her plasma renin activity was 5.31 mg/l/s (normal: up to 1.7). The diagnosis of adrenal insufficiency was made and she was commenced on cortisol and 9 fluorocortisol replacement which induced clinical improvement. Her linear growth pattern (Figure 1) had been following a growth pattern just below the 5th percentile. At 9 years of age, however, her height and linear growth velocity started to slow down and fell below the 5th percentile. Her linear growth velocity at 12 years of age was 5.78 cm per year which was subnormal for her age and stage of puberty (Tanner stage II for breast development and I for pubic hair). The bone age was 10 years at the chronological age of 12½ years (2SD = 28 months).

Growth hormone provocative testing was carried out after ensuring that she was on optimal treatment and was biochemically euthyroid. Serial samples during night sleep at one hour interval showed a peak value of 5 ug/L 2 hours after the onset of sleep (other values were <1, <1, <1, 1, <1 and 2 ug/L). Serum

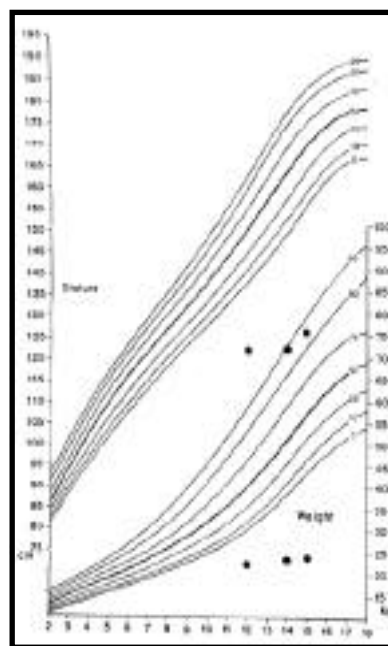


Figure 1 - The growth chart of patient number 2.

growth hormone values after 15 grams of intravenous arginine were: <1, <1, <1, 1, 3, 2 and 1 ug/L and after 250 mg of oral L-dopa and 20 mg oral propranolol were <1, <1, <1, <1, 2, <1 ug/L. She was started on biosynthetic human growth hormone treatment. Her linear growth velocity improved with a calculated linear growth velocity of 6.5, 5.5, 4.9, 3.8 cm per year at 13, 14, 15 and 16½ years of age. Her pubertal status was Tanner stage 4 for breast and pubic hair development. Her father's height was 165 cm and mother 152.5 cm giving her a midparental height of 152.5 cm. Her younger brother developed the same condition (mucocutaneous candidiasis at 4 years of age, hypoparathyroidism at 7½ years of age, and Addison's disease at 12 years of age). He however, continued to have normal growth pattern. A 2-year-old paternal cousin has mucocutaneous candidiasis but has shown no evidence of glandular involvement. The family history is otherwise negative for a similar illness. There is however, history of short stature in the family as paternal aunts were reported to be less than 150 cm in height. Growth hormone was discontinued when she achieved a height of 150.8 cm, breast development and pubic hair Tanner stage 4.

**Patient 2.** A 4-year-old Saudi boy presented at the age of 6 years with a history of 2 attacks of Carpopedal spasms. At that time a diagnosis of autoimmune hypoparathyroidism was entertained and was controlled with oral calcium as well as vitamin D<sub>3</sub>. At the age of 12 years, he developed epigastric pain which was associated with vomiting, generalized malaise as well as weakness. There was

loss of appetite and weight loss of 4 months duration. There was history of hyperpigmentation, dizziness, and photophobia. Physical examination showed that he was underweight and short for his age (Figure 2). Skin examination showed scattered hyperpigmented macules and papules distributed mainly on the lower and upper limbs and chest. The oral cavity had 3 white patches and the lips were hyperpigmented. Nails were normal. There were 2 hypopigmented areas over the left arm and right iliac crest. He has cortical cataract and keratitis on both eyes. An atrial septal defect (ASD) murmur was heard, physical examination was otherwise unremarkable. ACTH stimulation test showed cortisol values of 21.8, 20.3, 29.4, 34.7, and 29.9 mmol/L. He was therefore placed on hydrocortisone. Indicated by obvious slow growth velocity, provocative growth hormone stimulation test was performed. Growth hormone values were 9.5, 5.4, 1.0 and 1.5 ng/ml taken at 0, 30, 60, and 90 minutes, after 1 mg glucagon was given. They were 0.3, 2.3, 1.5, 0.8, and 4.3 ng/ml taken at 0, 30, 60, 90, and 120 minutes after clonidine was given, growth hormone values taken during sleep were 1.5, 0.32, and 1.4 at 1, 1½ hours post onset of sleep and at 5 a.m. Unfortunately growth hormone treatment was not feasible as he was from a remote area where constant growth hormone supply could not be assured.

At 14 years of age his TSH was elevated at 16.7 m/u/L and free T4 10.7 (N: 10-25 mmol/L). He was therefore commenced on L Thyroxine treatment.

**Discussion.** Short stature in children with autoimmune polyglandular disease type 1 is not rare.<sup>7</sup> Several factors may be contributing. The multiple medical problems these patients have, need meticulous attention and optimal therapy to achieve normal growth pattern. Adequate nutrition is always warranted in children with chronic illness. This was monitored in the children presented and they continued to show adequate weight gain throughout follow-up with the exception of the time prior to diagnosing them to have adrenal insufficiency. Linear growth, however, started to decelerate at 9 years in the first case, and at 13.5 years of age in the second.

Pituitary gland involvement in autoimmune polyglandular disease type 1 is extremely rare. The nature of the disease, however, allows this to stand as a possibility. Central diabetes insipidus was reported in one case.<sup>8</sup> The poor growth velocity, delayed bone age and the nature of the disease in addition to excluding the other possible causes of short stature in this set up made it essential to subject these children to growth hormone provocative testing. Standard growth hormone testing confirmed the diagnosis of growth hormone deficiency.<sup>9-10</sup> Furthermore, the response to growth hormone therapy was satisfactory in the first case. This in the absence of a single

reliable diagnostic test for growth hormone deficiency, also further confirms the diagnosis.<sup>11</sup> This response was also associated with normal pubertal progress towards the end of her puberty with the achievement of an acceptable ultimate height which is compatible with her potential. Primary ovarian failure is a possibility in these cases. This was not evident in this case. Prediction of this possibility before puberty may not be possible as pubertal prognosis in the presence of elevated serum gonadotropins in girls with this condition have been reported.<sup>12</sup>

The first patient had a brother and a cousin who also had the same condition. The former has not shown evidence of growth failure and has achieved a normal height for his age. The latter is too young to draw any conclusion as evidence of having glandular involvement of other siblings. Assessment of them was not feasible. The heredity of this condition is also interesting. HLA association has been established.<sup>13</sup> Furthermore, the individual components of this condition may also be HLA associated.<sup>14</sup> The progressive nature of various components of this condition leads to a necessary and continuous awareness and anticipation of these associations.<sup>15</sup>

We conclude that autoimmune polyglandular disease type 1 can be associated with growth hormone deficiency. This is an important defect which needs to be diagnosed and treated properly.

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## References

1. Thorpe ES Jr, Handley HE. Chronic mycelial stomatitis in a child aged four and one-half years. *Am J Dis Child* 1929; 38: 328-338.
2. Gass JDM. The syndrome of keratoconjunctivitis, superficial moniliasis, idiopathic hypoparathyroidism and Addison's disease. *Am J Ophthalmol* 1962; 54: 660-674.
3. Ahonen P, Myllirniemi S, Sipila I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy (ACEPED) in a series of 69 patients. *N Engl J Med* 1990; 322: 1829-1836.
4. Neufield M, Maclaren N, Blizzard R. Autoimmune polyglandular syndromes. *Pediatr Ann* 1980; 154-162.
5. Wagman RD, Kazdan JJ, Kooh SW, Fraser D. Keratitis associated with the multiple endocrine deficiency, autoimmune disease, and candidiasis syndrome. *Am J Ophthalmol* 1987; 103: 569-575.
6. Myllirniemi S, Perheentupa J. Oral findings in the autoimmune polyendocrinopathy-candidosis syndrome (APECS) and other forms of hypoparathyroidism. *Oral Surg* 1978; 45: 721-729.
7. Jayakumar RV, Subesinghe N, Sulimani RA, Mekki MO, Al-Nuaim AR, Abdullah MA. The autoimmune polyglandular syndrome in Saudi Arabia: A study of 12 cases. *Saudi Medical Journal* 1989; 10: 206-209.
8. Clifton-Bligh P, Lee C, Smith H, Posen S. The association of diabetes insipidus with hypoparathyroidism, Addison's disease, and mucocutaneous candidiasis. *Aust N Z J Med* 1980; 10: 548-551.

9. Spandoni GL, Cianfarani S, Bernardini S, Vaccaro F, Galasso C, Manca Bitti ML et al. Twelve-hour spontaneous nocturnal growth hormone secretion in growth retarded patients. *Clin Pediatr* 1988; 27: 473-478.
10. Preece MA. Diagnosis and treatment of children with growth hormone deficiency. *Clin Endocrinol Metab* 1982; 11: 1-24.
11. A report by the Drug and Therapeutic Committee of the Lawson Wilkin's Pediatric Society. Guidelines for the use of growth hormone in children with short stature. *J Pediatr* 1995; 127: 857-867.
12. Lucky AW, Rebar RW, Blizzard RM, Goren EM. Pubertal progression in the presence of elevated serum gonadotropins in girls with multiple endocrine deficiency. *J Clin Endocrinol Metab* 1977; 45: 673-678.
13. Ahonen P, Koskimies S, Lokki ML, Tiilikainen A, Perheentupa J. The expression of autoimmune polyglandular disease type 1 appears associated with several HLA-A antigens but not with HLA-DR. *J Clin Endocrinol Metab* 1988; 66: 1152-1157.
14. Maclaren NK, Riley WJ. Inherited susceptibility to autoimmune. Addison's disease is linked to human leukocyte antigens-DR3 and/or DR4, except when associated with type I autoimmune polyglandular syndrome. *J Clin Endocrinol Metab* 1982; 54: 846-868.
15. Saenger P, Levine LS, Irvine WJ, Gottesdiener K, Rauh W, Sonino N et al. Progressive adrenal failure in polyglandular autoimmune disease. *J Clin Endocrinol Metab* 1982; 54: 863-868.