Attainment of normal height in severe juvenile hypothyroidism

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Abstract

Prolonged juvenile hypothyroidism results in a permanent loss in height that is related to the duration of thyroxine deficiency before adequate thyroxine replacement treatment. A 13 year old girl with severe juvenile hypothyroidism was studied prospectively. She had an undetectable serum thyroxine concentration, a height SD score of -6.6 SD, and a bone age of 5.8 years. The enlarged pituitary gland involuted with thyroxine treatment to produce an empty sella. In addition to thyroxine the girl was treated with a gonadotrophin releasing hormone agonist to avoid the progression of puberty for 18 months and with growth hormone to achieve normal adult height. (Arch Dis Child 1994; 70: 429–431)

The permanent loss in height related to the duration of thyroxine deficiency in juvenile hypothyroidism has been reported by several authors.^{1–3} Rivkees *et al*¹ and Harada *et al*² found that only 70% catch-up growth is generally achieved with thyroxine replacement. Explanations for compromised adult stature are overtreatment, reduced potential for catch-up growth induced by hypothyroidism, and puberty's limiting effect on residual bone growth.

Methods

Serum luteinising hormone, follicle stimulating hormone (FSH), growth hormone, and thyroid stimulating hormone (TSH) were measured by two site immunoradiometric assay (Daiichi Radioisotope Co, Tokyo). Bone age was assessed by the Greulich and Pyle atlas.

Case report

Until the age of 6 years the girl studied showed an average gain in height but subsequently had a sudden reduction in height velocity (figure). At 13 years of age her height for chronological age (SD score) was -6.6 SD and her bone age 5.8 years. She had overt hypothyroidism, dry coarse skin, and no sign of pubertal development. Serum thyroxine was undetectable and TSH concentration was 510 mU/l. Autoantibodies to microsomal antigens and thyroglobulin were negative. Her TSH receptor antibody level was 6.7% (normal less than 10%). An atrophic thyroid gland was confirmed by ultrasonography. Cranial magnetic resonance imaging (MRI) revealed an enlarged pituitary gland (78 mm²; normal 22–45 mm²) at diagnosis.

On the basis of the abrupt onset of hypothyroid symptoms in a previously normal child at 6 years, the thyroid function tests and atrophic thyroid gland, the patient was diagnosed as having juvenile hypothyroidism of 7 years' duration. She was treated with thyroxine, and the dose was thereafter adjusted to maintain normal thyroxine and TSH concentrations (figure). The enlarged pituitary gland involuted after suppression of TSH secretion, resulting in an empty sella and small pituitary size (22 mm²) detected by cranial MRI. The peak growth hormone concentrations in response to a growth hormone releasing factor were 8.4 µg/l (before thyroxine treatment) and 22.4 µg/l (three months after thyroxine). She gained 16 cm in height during the first 14

Growth curve in relation to treatment.

months of thyroxine replacement, and her bone age advanced to 12 years by chronological age 14.6 years. Puberty commenced at 14.7 years (basal-peak values in response to 100 µg gonadotrophin releasing hormone (GnRH) infusion: luteinising hormone, 2.8–14.5 IU/l; FSH, 7.3–14.0 IU/l) and threatened to compromise her potential height gain. We therefore administered intranasal GnRH agonist treatment (buserelin 1800 µg/day four times a day) between 14.7 and 16.2 years. At the age of 15.3 years her bone age was 12.5 years and the change in bone age/height age during the combination treatment was 1.0. During this regimen growth hormone secretion was impaired: peak values of growth hormone in response to insulin and arginine were both less than 7 µg/l. The patient was therefore treated with daily growth hormone injections (0.5 IU/kg/week) in addition to thyroxine and GnRH agonist from age 15.3 until 17 years. Menarche was noted three months after stopping GnRH agonist. At 17 years of age her height and bone age were 155 cm (−0.56 SD score) and 14 years, respectively. The mid-parental height is 163 cm.

Discussion

Compromised adult stature is related to the duration of severe hypothyroidism.^{1–3} Our patient had severe hypothyroidism for seven years and a height SD score of −0.6 when she had previously been of average height. According to the previous reports^{1,2} her adult height deficit was therefore predicted to be approximately 17 cm despite adequate thyroxine replacement.

After the start of thyroxine treatment most patients' catch-up growth occurs during the first three years and is accompanied by marked advance of bone age. Our patient also showed an early disproportionate effect of thyroid hormone on bone age maturation. This disproportionate bone age maturation may contribute to the predicted loss of adult stature; however, this conclusion is contingent on the accuracy of skeletal age determination at diagnosis and on treatment.³ Hypothyroidism disproportionately affects the epiphyses, and bone age assessment by comparison with the morphology of the epiphyses and its relationship with the metaphysis yields a low score.³

The higher average age of children with juvenile hypothyroidism makes their catch-up difficult to achieve because of shorter period of residual growth. In a parallel situation, average final height in isolated growth hormone deficiency is significantly lower than that in growth hormone plus gonadotrophin deficiency.⁴ One strategy to overcome this is to administer a relatively large dose of growth hormone during puberty to improve adult stature.⁵ Another is to provide gonadal suppression treatment if inappropriate pubertal progression threatens catch-up growth.⁴

The origin of an empty sella is an arachnoidal diverticulum containing cerebrospinal fluid in the pituitary fossa. Until recently

the empty sella was believed to have minimal clinical significance; however, recent observations suggest that it is frequently associated with growth hormone deficiency.⁶ In juvenile hypothyroidism, low growth hormone production has not been considered to be a major factor in incomplete catch-up growth.^{1,2} However, we found impaired growth hormone secretion in this patient during gonadal suppression treatment and have demonstrated height gain with growth hormone treatment. Recent observation suggests a contribution of growth hormone deficiency to bone lesions in hypothyroidism. Growth hormone plus GnRH agonist treatment contributed to an improvement in height gain in this girl.

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Commentary

There is much of the pattern of both growth and pubertal maturation in primary juvenile hypothyroidism that requires further study. Contrary to commonly held beliefs and despite the usual findings of a severely delayed bone age, growth failure in primary juvenile hypothyroidism is not fully reversible with the onset of thyroxine treatment.^{1,2} There are difficulties with the interpretation of data on height prediction in primary hypothyroidism as this depends on bone age scoring systems, which are unreliable because of the disturbance of epiphysal compared with metaphysal morphology. However, final height outcome is unsatisfactory when compared with parental centiles.^{1,2} Previous work, using the suppression of serum TSH, suggests that a replacement dose of thyroxine of 100 µg/m²/day is optimal but this probably requires reassessment. Certainly compliance to chronic treatment regimens, especially during adolescence, is always difficult to assess.

Puberty in primary hypothyroidism may be dysconsonant either in the relationship between the acquisition of various modalities of sexual maturation or in the timing of the events of puberty. The latter is illustrated in that, even though there is an abnormally prolonged growth acceleration of postmenarche girls with primary hypothyroidism on replacement thyroxine treatment, this does not restore normal height prognosis.² Puberty is usually delayed and occurs at the limit of the normal range,² although this may be considered early in relation to bone age. It is important to consider whether sexual maturation is consonant as some