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CASE REPORT

Reversible growth failure and complete GH deficiency in a 4-year-old girl with very early Hashimoto's thyroiditis and subsequent hyperplasia of pituitary thyrotroph cells

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Abstract Hashimoto's thyroiditis is a well-known cause of growth retardation in adolescence. It is less frequently seen in children and rarely seen in infants. A 4-year-old girl was referred to our clinic for a second opinion before starting growth hormone (GH) treatment. Linear growth had markedly declined in the past 2 years, with height −3.4 standard deviations. GH deficiency was complete. She had dry, gray-sallow skin and bloated abdomen, but no goiter. The parents reported fatigue and constipation. Hormonal evaluation revealed TSH 629.5 mIU/ml, free T4 0.08 ng/dl, and prolactin 17.2 ng/ml. Bone age was 2 years. Antibodies to thyroglobulin and thyroid peroxidase were positive, suggesting Hashimoto's thyroiditis. Brain magnetic resonance imaging showed anterior pituitary hyperplasia. After 3 years of L-thyroxine therapy, she was symptomless, her height was −0.6 standard deviations, and the TSH level was normal. Brain magnetic resonance imaging showed regression of the pituitary hyperplasia.

Conclusions: This report describes a patient with Hashimoto's thyroiditis and pituitary hyperplasia, both quite rare in very young children. Acquired hypothyroidism may appear after neonatal screening and therefore should not be overlooked in investigations of short stature, even when clinical signs of hypothyroidism are absent.

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What is Known:
- *Hashimoto's thyroiditis and pituitary hyperplasia are rare in very young children.*
- *Acquired hypothyroidism can appear after negative neonatal screening and should not be overlooked.*

What is New:
- *Short children should be evaluated for growth hormone deficiency but only after excluding other causes, particularly hypothyroidism, as we report a child with this disease but no clinical signs of it.*

Keywords Hypothyroidism · Pituitary hyperplasia · Growth hormone deficiency

Abbreviations

GHD	GH deficiency
HT	Hashimoto's thyroiditis
SD	Standard deviations
MRI	Magnetic resonance imaging

Background

Hypothyroidism is a well-known cause of growth retardation in children. Growth hormone deficiency (GHD) in children with height more than 2 standard deviations (SD) below the population mean should therefore not be evaluated until other causes of growth failure, especially hypothyroidism, have been excluded [5].

When hypothyroidism is prolonged and/or severe, pituitary hyperplasia may also manifest but it usually resolves after thyroxine therapy [1, 9].

We report for the first time a case of pituitary hyperplasia mimicking pituitary macroadenoma and complete GHD in a 4-year-old girl. She presented unrecognized Hashimoto's thyroiditis (HT), which apparently had begun 2 years earlier when growth velocity decreased.

Case presentation

A 4-year-old girl with severe short stature was referred to our clinic for a second opinion before starting GH treatment. Medical records revealed that the patient's mother had HT during her pregnancy, and the newborn screening tests in the first week of life were normal. The child's past medical and surgical history was unremarkable, but the parents reported she had experienced fatigue, constipation, and frequent abdominal pain in the last year.

Her height was −3.4 SD, whereas the mid-parental height was −0.2 SD, and her linear growth had markedly declined since the age of 2 years (Fig. 1). Hormonal evaluation performed by another clinician revealed low IGF1 (undetectable; n.v. 20–300 ng/ml) and IGFBP3 (undetectable; n.v. 800–3700 ng/ml), along with complete GHD (<3 mU/L for 2 stimulation tests) [5]. GH therapy was prescribed.

Clinical examination revealed a prepubertal girl with normal neurological development but slowed mentation. She presented gray-sallow skin and bloated abdomen but no goiter.

Hormonal evaluation in our clinic revealed TSH 629.5 mIU/ml (n.v. 0.27–4.2 mUI/l; Roche, Boulogne-Billancourt, France), free T4 0.08 ng/dl (n.v. 0.93–1.7 ng/ml; Roche, Boulogne-Billancourt, France), and prolactin 17.2 ng/ml (n.v. 2–20 ng/ml; Brahms, Clichy, France). IGF1 (n.v. 20–300 ng/ml; Siemens, Saint-Denis, France) and IGFBP3 (n.v. 800–3700 ng/ml; Siemens, Saint-Denis, France) were undetectable. Bone age was 2 years using the Greulich and Pyle method. Antibodies to thyroglobulin and thyroid peroxidase were positive, respectively, 1291 and 1289 UI/ml (n.v. < 130 UI/ml), suggesting HT.

Other causes of growth failure, like chronic systemic diseases, celiac disease, and skeletal disorders, were excluded. Karyotyping and psychological testing were not performed.

Thyroid ultrasound revealed an abnormal echotexture, with multiple hypoechoic micronodules but normal parenchyma, suggesting HT. Pelvic ultrasound results were normal, eliminating cysts as the cause of her frequent abdominal pain.

Brain magnetic resonance imaging (MRI) ruled out an organic lesion but showed an 11-mm enlargement of the anterior pituitary (Fig. 2) and a pineal cyst of less than 12 mm.

After 4 months of L-thyroxine therapy at 50 μg/day, she presented no signs or symptoms suggestive of hypothyroidism. Growth velocity was accelerated (1 cm/month) (Fig. 1), and her physical and mental activities were improved.

After 1 year of treatment, height was −2.6 SD, with a gain of 10 cm/year (Fig. 1). Hormonal evaluation revealed TSH 2.4 mIU/ml, free T4 1.71 ng/dl, and prolactin 3.2 ng/ml. IGF1 and IGFBP3 were, respectively, 150.0 and 3890 ng/ml. MRI showed a regression of the pituitary hyperplasia, with the anterior pituitary measuring 5 mm.

At the last consultation, she was 7.6 years old and her height was −0.6 SD, for a gain of 27 cm during the 3 years of L-thyroxine therapy (Fig. 1). Tanner stage was I, with no breast development or pubic hair, and bone age was 5.8 years, using the Greulich and Pyle method.

Discussion

Hashimoto's thyroiditis is a common cause of hypothyroidism in adolescence. It is less frequently seen in children and is very rare under the age of 3 years. A recent epidemiological study in a sample of 1387 Spanish subjects between 1 and 16 years old showed the prevalence of autoimmune thyroiditis to be 3.2 % between 12 and 16 years, 1.2 % between 6 and 12 years, and 0 % between 1 and 6 years [3].

Even when newborn screening for congenital hypothyroidism is negative, hypothyroidism may develop later in infancy. Moreover, neonates born to mothers with HT need close thyroid monitoring since they have a 32-fold increased risk of developing immunothyroiditis, supporting the evidence for genetic susceptibility [2].

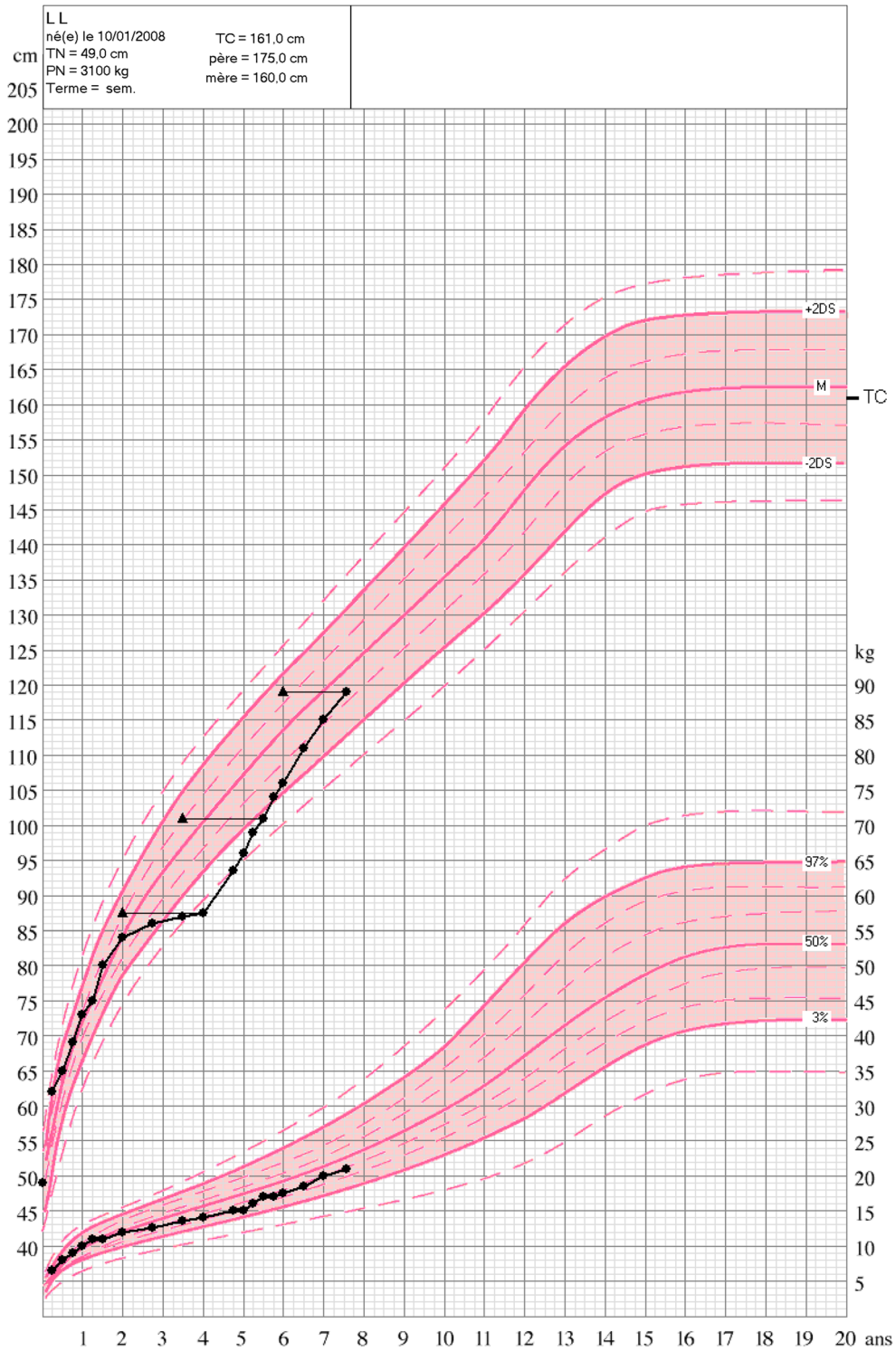

Fig. 1 Height and weight chart for our patient. Growth deceleration began at 24 months. Following the onset of L-thyroxine treatment at 4 years of age, growth velocity markedly increased with a gain of about 10 cm/year. Bone age was delayed by 2 years at 4 years of age and by 1.8 years at 7.6 years of age (*horizontal arrow*)

Pediatric cases of pituitary hyperplasia secondary to hypothyroidism have been reported, but the literature reveals only two cases in children under 8 years: the first was a 5.5-year-old girl with vaginal bleeding only [1], and the second was a 6.8-year-old girl with growth retardation and weight gain but no neurological symtoms [9]. This indicates the wide spectrum of clinical signs of severe hypothyroidism in children [6].

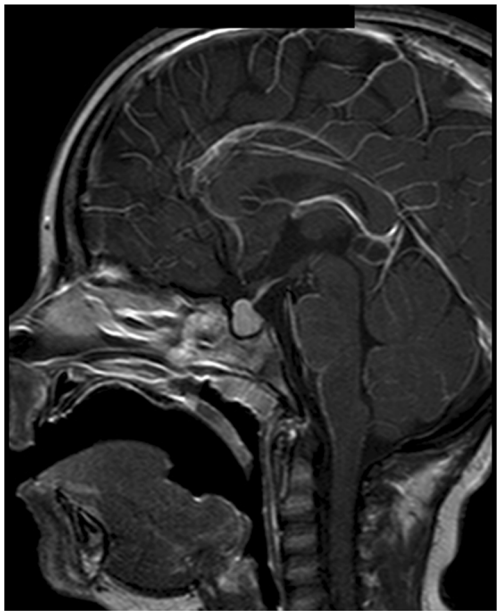

Fig. 2 Enlarged pituitary gland at presentation (sagittal views). The enlarged anterior pituitary gland measured 11 mm. The enlarged area was isointense to white matter on the T1 and T2 images. The mass enhanced homogeneously after gadolinium injection. A pineal cyst of less than 12 mm was also detected

Several mechanisms may contribute to growth failure in children with severe hypothyroidism, including the direct action of low thyroxine on the growth plate and skeletal growth and the secondary reductions in GH synthesis and secretion and IGF1 concentration. In hypothyroid rats, the width of the epiphyseal growth plate cartilage decreased by 27 % and that of articular cartilage by 35 %; epiphyseal trabecular bone volume decreased by 30 % and metaphyseal trabecular bone volume decreased by 66 % compared with age-matched control tissues [7]. Other experimental studies have shown that long-term hypothyroidism markedly reduces hypothalamic GHRH and GHRH-R gene expression and results in subsequent GH deficiency [4, 8].

Clinical vigilance, especially in the children of mothers with HT, is important to detect any cases of congenital hypothyroidism that were missed, as well as the rare cases of acquired hypothyroidism appearing before the age of 3 years. Despite negative screening results for hypothyroidism in newborns, acquired hypothyroidism can appear early in life and should not be overlooked in investigations of short stature, even in the absence of clinical signs.

Authors' contributions C. Sultan was responsible for patient care as head of the pediatric endocrinology unit and edited the manuscript; L Gaspari was responsible for patient care and wrote the manuscript; F Paris carried out the hormonal analysis and edited the manuscript; A Bonafé carried out the brain magnetic resonance imaging and bone age assessment and edited the manuscript; N Leboucq carried out the brain magnetic resonance imaging.

Compliance with ethical standards

Consent The patient's parents gave written informed consent for publication of this case report and any accompanying images.

Conflict of interest The authors declare that they have no competing interests.

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