CASE REPORT

Metrorrhagia and precocious puberty revealing primary hypothyroidism in a child with Down's syndrome

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We report a child with Down's syndrome in whom metrorrhagia and precocious puberty revealed primary autoimmune hypothyroidism. The patient had a decreased growth velocity, exaggerated weight gain, bone age delay, and bilaterally enlarged multicystic ovaries. Delays in the diagnosis and treatment of hypothyroidism can lead to this peculiar presentation.

Severe hypothyroidism is a rare cause of precocious puberty.¹ We report the case of a 7 year old girl with Down's syndrome diagnosed with chronic autoimmune thyroiditis who presented with metrorrhagia, precocious puberty, and enlarged multicystic ovaries.

CASE REPORT

Our patient had the typical morphological features of Down's syndrome. She presented at the age of 7 years and 4 months with a three week history of severe metrorrhagia. Breast development had been noticed by the child's parents a week before the onset of metrorrhagia. They denied any recent changes in their daughter's behaviour.

The patient had stable haemodynamic parameters. Growth velocity was decreased and contrasted with exaggerated weight gain (fig 1).² Pubertal development was rated B2P1A1 with reference to Tanner stages with signs of oestrogenisation of the external genitalia.³ The thyroid gland was not enlarged and there were no other clinical abnormalities.

Laboratory findings included haemoglobin 111 g/l and a normal coagulation profile. Response to the gonadotropin releasing hormone (GnRH) test was blunted, with plasma luteinising hormone (LH) concentrations remaining low at 0.2 IU/l and follicle stimulating hormone (FSH) concentrations rising slightly from 4.2 IU/l to 4.7 IU/l. Plasma oestradiol was high at 98 pg/ml in relation to the patient's chronological age (normal: 2-15 pg/ml) and to her pubertal stage (normal: 10-33 pg/ml). Plasma thyroid stimulating hormone (TSH) concentrations were raised at 792 mIU/l (normal: 0.5-4 mIU/l), plasma free thyroxine concentration was low at 3 pmol/l (normal: 10-20 pmol/l), and antithyroperoxidase antibodies were strongly positive. Plasma prolactin was high at 33 ng/ml (normal: 2-18 ng/ml).

Bone age was estimated at 6 years using the Greulich and Pyle method.⁴ Pelvic ultrasonography (fig 2) revealed bilaterally enlarged multicystic ovaries (the left ovary measuring 70×39 mm, the right ovary 45×29 mm), with a uterus of pubertal dimensions (length 66 mm). Neck ultrasonography revealed a normal sized hypoechogenic and micronodular thyroid gland.

These results were consistent with the diagnosis of primary hypothyroidism as a result of chronic autoimmune thyroiditis. Severe hypothyroidism was associated with hyperstimulation of the ovaries, resulting in metrorrhagia and precocious

Figure 1 The patient's growth chart. The arrow indicates the beginning of thyroxine replacement therapy.

puberty. Symptomatic treatment with tranexamic acid and cyproterone acetate stopped the metrorrhagia in 48 hours. Treatment with thyroxine (50 µg/day) led to the regression of breast development and normalisation of the ultrasound abnormalities of the ovaries when the patient was assessed a month later.

DISCUSSION

In our patient, severe primary hypothyroidism caused by chronic autoimmune thyroiditis, which was undiagnosed for months, was revealed by metrorrhagia and precocious puberty. The diagnostic delay regarding hypothyroidism can be attributed in part to the association with Down's syndrome, in which case cognitive impairment and behavioural changes may be less easily identified than in other children. On the other hand, this syndrome predisposes to autoimmune disorders, including chronic autoimmune thyroiditis.⁵ Decreased growth velocity and bone age delay, unusual in precocious

Abbreviations: FSH, follicle stimulating hormone; LH, luteinising hormone; TRH, TSH releasing hormone; TSH, thyroid stimulating hormone

Figure 2 Ultrasound scan of (A) the left ovary (measuring 70×39 mm), and (B) the right ovary (measuring 45×29 mm). The ovaries are notably enlarged and multicystic in aspect.

puberty, associated with exaggerated weight increase, suggested the diagnosis of hypothyroidism. The bilaterally enlarged and multicystic ovaries were suggestive of ovarian hyperstimulation rather than of autonomous endocrine ovarian activity as seen in secreting ovarian tumours (in which case a single unilateral lesion is the usual finding). The low LH concentrations and measurable but relatively low FSH concentrations, show that this hyperstimulation bypassed the gonadotropin-ovarian axis and involved TSH, notably increased in our patient, and known, at high concentrations, to induce precocious puberty.¹ Prolactin concentrations were, as in similar observations, high, as this hormone and TSH share the same hypothalamic releasing factor, TSH releasing hormone (TRH).¹ Continuous and high TRH concentrations have been shown to stimulate FSH secretion as well, and this overlap at the level of the pituitary gland has been cited as the cause of precocious puberty in similar observations.⁶ In our patient, although this overlap is supported by measurable FSH concentrations, these are relatively low given the degree of ovarian hyperstimulation and are unlikely to represent the only link between primary hypothyroidism and precocious puberty.⁷

In vitro studies have shown that supraphysiological TSH concentrations induce the cellular response obtained by FSH, as if both hormones acted through the FSH receptor.⁷ Thus, very high TSH concentrations activate the gonads through an FSH-like effect, explaining similar observations of the predominance of FSH mediated functions (ovarian hyperstimulation in girls, enlarged testes without other signs of virilisation in boys) over LH mediated functions.¹

In conclusion, children with precocious puberty having decreased growth velocity and bone age delay should be assessed for hypothyroidism. Delays in the diagnosis and the treatment of hypothyroidism can lead to this peculiar presen-

tation. Special attention should be given to children with Down's syndrome, who are more at risk of thyroid disease than other children, and whose thyroid function should be assessed in case of decreased growth velocity, exaggerated weight gain, and/or precocious puberty.

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