Thyroid ultrasonography in congenital isolated thyroid stimulating hormone deficiency

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Abstract

The effects of thyroid stimulating hormone (TSH) deficiency on thyroid development was examined using ultrasonography in a child with congenital isolated TSH deficiency. Ultrasound revealed the thyroid gland was one sixth normal volume, suggesting that TSH plays an important part in thyroid growth, but not a critical role in differentiation.

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Keywords: thyroid stimulating hormone deficiency, thyroid ultrasonography, thyroid growth.

Congenital isolated thyroid stimulating hormone (TSH) deficiency is a rare autosomal recessive disease characterised by typical signs and symptoms of cretinism. It has been shown that congenital isolated TSH deficiency in Japan is caused by a point mutation in the codon for the 29th amino acid of the TSH beta subunit. This results in conformational changes of the beta subunit that preclude its association with the alpha subunit.^{1,2} The disease provides a model for considering the effects of TSH on how the thyroid gland develops. We describe a child with congenital isolated TSH deficiency whose thyroid gland was found to be hypoplastic on ultrasound examination.

Case report

The patient was a 10 year old girl whose congenital hypothyroidism had been diagnosed as a neonate. She had been born after an uncomplicated full term pregnancy and delivery and

weighed 2983 g. The patient was admitted to our hospital at 10 days of age because of jaundice and poor appetite. Thyroid hormone studies showed a depressed triiodothyronine uptake of 19% (normal range 25–35), a thyroxine concentration of 34.7 nmol/l (72.1–139.0), and TSH of 2 mU/l (<12). Scintigraphy and thyrotrophin releasing hormone (TRH) stimulation test were not performed. Thereafter, she was treated with standard therapeutic doses of L-thyroxine, monitored periodically by determining the serum concentration of thyroxine. At 10 years of age, the dosage of L-thyroxine was gradually tapered for six months to exclude the possibility of transient hypothyroidism, but serum concentrations of thyroxine and TSH remained low and the patient complained of fatigue. Before the dose of L-thyroxine was increased, TRH stimulation test, luteinising hormone releasing hormone stimulation test, and insulin provocative growth hormone secretion test were performed. The results of these disclosed adequate secretion of hormones other than TSH, indicating that the most likely diagnosis was congenital isolated TSH deficiency.

Methods and results

DNA ANALYSIS

Genomic DNAs were extracted from peripheral blood by standard techniques. Polymerase chain reaction (PCR) and MaeI digestion were carried out as previously reported³ with modification. In summary, a 0.85 kb fragment of the TSH β gene was amplified by 30 cycles of PCR using pTSH621p and pTSH1471r. After digestion with MaeI, the PCR products were analysed by electrophoresis on 2% agarose gel containing ethidium bromide, then photographed. A 0.85 kb fragment produced by PCR was cleaved into two fragments of 0.71 kb and 0.14 kb only when it harboured a missense mutation from a codon GGA (glycine) to AGA (arginine), generating a *de novo* MaeI cleavage site. As shown in the figure, the MaeI cleavage profile of PCR products showed that the patient was homozygous, whereas other family members were heterozygous, with respect to the mutated allele.

ULTRASONOGRAPHY

The ultrasonic scanner used was an Aloka SSD-650 unit (Aloka Co) equipped with real time 5.0 MHz and 7.5 MHz transducers. The child was placed supine with her neck hyperextended to measure the long axis diameter (D1), the short axis diameter (D2), and the

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MaeI cleavage profiles of PCR products. Genomic DNAs extracted from peripheral blood were analysed by PCR using pTSH621p and pTSH1471r followed by MaeI digestion.

thickness (D3) of both lobes and the isthmus. The measured values were (cm): isthmus, D1=1.0, D2=0.7, D3=0.2; right lobe, D1=1.8, D2=0.7, D3=0.2; and left lobe, D1=2.3, D2=1.0, D3=0.7. As in Ueda's study,⁴ the volume of the thyroid gland was determined using a standard geometric formula, in which each lobe of the thyroid gland was assumed to be a prolated spheroid (volume of a prolated spheroid= $D1 \times D2 \times D3 \times \pi/6$). The total volume of the patient's thyroid gland was calculated as the sum of each lobe. The result was 1.04 cm³, obviously a small thyroid gland compared with the thyroid gland size derived from healthy children with the same body height (mean (SD) 6.3 (2.0) cm³).

Discussion

There are fundamental questions about the control of thyroid cell growth and multiplication and differentiation.⁵ In our patient we confirmed that TSH has a developmental role in thyroid growth. It is true that goitre is induced by an increased TSH concentration in response to any interference with thyroid hormone secretion or synthesis, such as iodine deficiency, but there have been methodological difficulties in evaluating how TSH acts on fetal thyroid development. With ultrasonography, however, we could examine the effects of TSH on the developing thyroid gland in this child in

whom TSH had been deficient since the fetal stage. In studies of aborted human fetuses, thyroid hormone synthesis has been demonstrated in the 11th week, whereas pituitary TSH was detected at 8–10 weeks and serum TSH at 10–12 weeks,⁶ showing that TSH plays a minimal part in the differentiation of the thyroid gland.

Our ultrasound study of this patient revealed a hypoplastic thyroid gland of one sixth normal volume. Although findings in a single case must be interpreted with caution, we conclude that TSH plays an important part in thyroid growth and function, but that it is not indispensable for differentiation.

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