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Correspondence to Dr I Amitai, Paediatric Department, Hadassah University Hospital, Mount Scopus, POB 24035, Jerusalem 91240, Israel.

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Congenital isolated thyrotrophin releasing hormone deficiency

H NIIMI, H INOMATA, N SASAKI, AND H NAKAJIMA

Department of Paediatrics, School of Medicine, Chiba University, Chiba, Japan

SUMMARY A 4½-year-old girl with congenital thyrotrophin-releasing hormone (TRH) deficiency is described. Oral TRH administration led to normal thyroid hormone and TRH levels in the blood; favourable growth and development was achieved.

Deficiency of thyroid-stimulating hormone (TSH) and hypothyroidism can occur in any condition that is associated with developmental defects of the pituitary or hypothalamus, or in children with idiopathic hypopituitarism. However isolated deficiency of TSH, or thyrotrophin-releasing hormone (TRH) is rare.^{1,2} We describe in detail a case of isolated TRH deficiency.

Case report

A 4½ year-old girl was referred to us because she was short.

She was the third child of healthy, intelligent parents. Pregnancy and delivery had been normal, as had been the neonatal period. Birthweight was 3200 g and length 50 cm. Growth to age 1 year had apparently been normal but retardation of growth was noticed at 2–3 years of age.

Her parents were not related, but her maternal grandparents were consanguineous. There was no family history of thyroid disease, dwarfism, or mental abnormality.

Physical examinations showed height 93.0 cm (–2.0 SD of the mean height for Japanese girls as reported by the Japanese Ministry of Health and Welfare), weight 13.0 kg (–1.6 SD), with normal body proportions. The thyroid gland was not enlarged, and the remainder of the physical examina-

tion was normal. Roentgenograms of the skull were normal and bone age was 2¾ years.

Haematological studies, urine analysis, and blood chemical determinations were normal. An electroencephalogram was normal. Computerised tomography scans of the skull were normal. Her developmental quotient was estimated to be 112.

At the initial visit, the serum thyroxine (T4) value was 4.1 µg/100 ml (52.8 nmol/l) (normal 4.5–13.5 µg/100 ml), serum tri-iodothyronine (T3) 177 ng/100 ml (2.7 nmol/l) (normal 98–202 ng/100 ml), and serum TSH 14 µU/ml (normal <2–8). Thyroid uptake of ¹²³I sodium iodide was 7.1% at 24 hours (normal 10–40%). A thyroid scan gave normal results. Tests for antithyroglobulin antibody and antimicrosome antibody were negative. The serum thyroxine binding globulin determined by radioimmunoassay was 20.3 µg/ml (338.3 nmol/l) (normal 15.7–43.3 µg/ml).

A peak TSH level of 70 µU/ml was obtained after administration of 130 µg (10 µg/kg) of TRH intravenously (normal 10–40 µU/ml). Two additional TRH tests showed similar positive responses. Luteinising hormone and follicle-stimulating hormone showed normal responses to intravenous injection of 40 µg of luteinising hormone-releasing hormone. Serum growth hormone was demonstrable in the fasting state (3.2 ng/ml), and an increase was obtained during insulin-induced hypoglycaemia (20.5 ng/ml). The plasma level of adrenocorticotrophin was 16 pg/ml (normal 15–85) in the early morning and a peak level of 27 pg/ml was obtained by insulin-induced hypoglycaemia. Urinary 17-OHCS were 3.9 mg and urinary 17-ketosteroids 0.1 mg/24 hours. Serum prolactin level was 16.4

ng/ml and a peak level of 101.7 ng/ml was obtained by TRH administration.

The concentration of serum TRH determined by radioimmunoassay³ was below the limit of detectability (<2 pg/ml). Methimazole (20 mg) was given for 10 days but the serum TRH still remained below 2 pg/ml without any increase in secretion. When 30 mg methimazole was given for 10 days to an adult in a TRH secretion stimulation test a peak level of >20 pg/ml was reached (T Mitsuma, 1979, personal communication).⁴

Discussion

Now that radioimmunoassay of pituitary hormones is possible, diagnosis of isolated deficiency of each of the pituitary hormones is based on firmer grounds than previously. Such developments have led to considerably more patients being diagnosed with hypothyroidism due to TRH deficiency among hypothyroid patients with pituitary dwarfism or organic disturbance of the hypothalamus. However, only a few cases of idiopathic isolated TRH deficiency have been reported, one probably due to congenital cause⁴ and two probably acquired postnatally.^{5,6} This case may be the first of isolated TRH deficiency confirmed by radioimmunoassay measurement of TRH to be reported.

A child with short stature and normal proportions, delayed bone age, no anaemia, and normal developmental quotient made us at first suspect pituitary dwarfism. Insulin loading however, successfully stimulated growth hormone secretion.

Levels of serum TSH were initially a little raised at 14 μ U/ml. T₄ was low at 4.1 μ g/100 ml with excessive response to TRH. Thyroidal ¹²³I uptake was 7.1% after 24 hours, which suggested hypothyroidism.

Antithyroid antibodies were negative and the thyroid gland was not enlarged. A thyroid scan gave normal results. Since serum T₃ level increased on TRH administration, as reported from some investigators, hypothyroidism in this patient was thought to be neither primary nor to be mediated by the pituitary.

A long-term follow-up without medication showed fluctuations of serum T₄ between the lower limit of normal and low normal levels. If levels of serum T₄ declined, levels of serum TSH increased with excessive response to TRH. A similar case in which isolated TRH deficiency was diagnosed in an adult patient in whom serum TSH was occasionally a little increased has been reported.⁵ The negative feedback mechanism in the pituitary-thyroid axis of these patients was probably maintained at normal. Pituitary hormones other than TSH increased to respective secretory stimuli: growth hormone,

adrenocorticotrophin, and cortisol to insulin, LH and FSH to luteinising hormone-releasing hormone, prolactin to TRH, with a slight delay in some of them.

TRH in the serum measured by radioimmunoassay, was below the limit of detection, and the level did not increase in a TRH secretion stimulation test.

This patient had no history of trauma nor did she have neurological abnormalities. Computerised tomography scans of the skull and electroencephalogram obtained in order to detect a possible organic lesion showed no abnormalities.

According to these findings, congenital isolated TRH deficiency probably caused hypothyroidism in this patient. TRH was therefore administered orally. Optimal dose of TRH appeared to be 4–6 mg/day orally. Serum TRH level was maintained within normal limits, 8–10 pg/ml (normal <2–60) and growth and development also proceeded normally. The body height, which had been –2.0 SD before treatment, became –1.0 SD after oral administration of TRH for 2 years and 8 months. Bone age also corresponds to chronological age at present.

In the hypothalamus, there is an enzyme for synthesising TRH according to some reports.⁷ In congenital TRH deficiency, this TRH synthesising enzyme is probably deficient.

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Correspondence to Dr H Niimi, Department of Paediatrics, School of Medicine, Chiba University, Inohanacho, Chiba 280, Japan.

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