Original

A Case with Hyperthyroidism Who Had Been Treated with Thyroid Hormone Because of Congenital Hypothyroidism

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Abstract. We encountered a case with hyperthyroidism at the age of 14 who had been diagnosed with congenital hypothyroidism (CH) and had received thyroid hormone replacement therapy. At the age of 16 d, the patient was referred to our hospital because of positive results at neonatal screening for CH. Serum level of TSH was 91.0 μ U/ml and serum level of T4 was 6.9 μ g/dl. The patient was diagnosed as having hypothyroidism, and hormone replacement therapy was started. Thereafter the dosage of thyroid hormone was adjusted and increased gradually as he grew to a maximum dose of 110 μ g/day at the age of 11. Until the age of 13, the patient's serum levels of TSH were within the normal range; then, at the age of 13 yr and 4 mo, his serum level of TSH dropped to a level below the detectable range. The dosage of administered thyroid hormone was tapered off and eventually eliminated at the age of 14. A thyroid scan and a radioactive iodine uptake test demonstrated a diffuse goiter with homogeneous uptake of radioactive iodine; the uptake rate was 60% at 24 h, and the serum level of TSH receptor antibody (TRAb) was 62.5% at that time. Administration of an antithyroid drug was started after confirmation that our patient had developed hyperthyroidism. There have been no case reports similar to our case.

Key words: congenital hypothyroidism, neonatal screening, hyperthyroidism

Introduction

Congenital hypothyroidism in neonates and very young infants is usually caused by thyroid dysgenesis associated with an absent, ectopic, or hypoplastic thyroid gland, and can be detected by neonatal screening in the general population. Although this illness itself is considered to be

unchanged throughout the patient's life, it can be transient in certain cases, for example, infants of mothers with chronic autoimmune thyroiditis (1).

Hypothyroidism in young children is mostly caused by chronic autoimmune thyroiditis, but it is quite rare before the age of 3 (2). Thomas *et al.* described four children, nine months to two years of age at the time of diagnosis, who had hypothyroidism that was most likely to have been caused by chronic autoimmune thyroiditis (3).

Hyperthyroidism is mostly due to an autoimmune disorder. TRAb, such as TSH-binding inhibitor immunoglobulin (TBII) and thyroid stimulating antibody (TSAb), have been detected

Received: December 8, 2004

Accepted: June 16, 2005

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in most patients with hyperthyroidism due to Graves' disease. Graves' disease and Hashimoto thyroiditis are encountered occasionally in the same patient. Takeda *et al.* reported a case who developed hyperthyroidism following hypothyroidism. In this patient TRAb changed from a blocking type to a stimulating type in association with the development of hyperthyroidism (4).

In this report, we describe a first case with hyperthyroidism, who was diagnosed with CH at neonatal screening and since then had been treated for 13 yr with thyroid hormone.

Case Report

The patient was born to unrelated parents. His mother was healthy, and his father had a clinical history of hyperthyroidism, which was treated with antithyroid drugs for one year when he was 42. The patient's birth weight was 2770 g, and his gestational age was 40 wk. At the age of 16 d, he was referred to our hospital because of positive results at neonatal screening for CH. The dried blood TSH at the ages of 5 and 12 d were 76.76 $\mu\text{U/ml}$ and 38.08 $\mu\text{U/ml}$, respectively. At the age of 16 d, the serum levels of TSH, T_4 and T_3 were 91.0 $\mu\text{U/ml}$ (adult normal range: 0.4–5.0), 6.9 $\mu\text{g/dl}$ (adult normal range: 3.7–12.1) and 1.36 ng/ml (adult normal range: 0.7–1.8), respectively. The patient was in good condition with slight jaundice. The size of the right distal femoral epiphysis was 6 $\times$ 3 mm and that of the left was 6.5 $\times$ 4 mm on X-ray examination. He was diagnosed with subclinical congenital hypothyroidism and received hormone replacement therapy from the age of 34 d. The initial dose was 15 mg of desiccated thyroid a day. At the age of 55 d, the patient's serum level of TSH was 38.5 $\mu\text{U/ml}$ and serum level of free T_4 was 0.94 ng/ml (adult normal range: 0.78–2.12). At the age of 18 mo, medication was ceased for 7 d and then a thyroid scan was performed. The scan demonstrated a thyroid gland normally located with homogeneous uptake of radioactive iodine;

the uptake rate was 15% (normal range, 10–40%) at 24 h. The potassium thiocyanate discharge test showed 25%, and a defect in iodine organification was suspected. Both growth and development were normal with therapy (Fig. 1). At the age of 3, both the serum level of anti-microsome antibody and anti-thyroglobulin antibody were negative. At the age of 6, the medication was changed to l-thyroxine from desiccated thyroid. At the age of 8, the patient's IQ score on WISC-R intelligence test was 133 (normal 105.4 $\pm$ 20.7), and his evaluated bone age was delayed one year compared with his chronological age. The dosage of l-thyroxine was gradually increased as he grew and the maximum dose was 110 $\mu\text{g/day}$ at the age of 11 (Fig. 2). Until the age of 13, the patient's serum levels of TSH were within the normal range. However, at the age of 13 yr and 4 mo, his serum level of TSH dropped to an undetectable level. The dosage of l-thyroxine was tapered off and eventually eliminated at the age of 14. The patient had general fatigue and emotional instability.

Physical findings at the age of 14 were as follows: height, 165.1 cm; weight, 50.2 kg; blood pressure, 124/63 mmHg; pulse rate, 109 beats/min.

Blood examination revealed the following data: free T_4 , 4.22 ng/dl (0.82–1.63); free T_3 , 12.0 pg/ml (2.0–4.9); TSH, less than 0.03 $\mu\text{U/ml}$ (0.41–4.01); TRAb, 62.5%; anti-microsome antibody, $\times$ 25600; anti-thyroglobulin antibody, negative.

A thyroid scan demonstrated a diffuse goiter with homogeneous uptake of radioactive iodine; the uptake rate was 60% at 24 h.

Having confirmed hyperthyroidism, therapy was started with antithyroid drugs (Fig. 3). The initial dosage of methimazole (MMI) was 20 mg/day. One month after that, the patient's serum level of free T_4 was normalized, and the dosage of MMI was tapered. Two months after the therapy, the patient's serum level of TSH had risen to a detectable level; however TRAb was still high, and the dosage of MMI was tapered again and l-thyroxine therapy was added.

Fig. 1 Growth chart. The patient's height and weight were almost the mean until the age of 11. His growth spurt started at about the age of 13 and his adolescence was of the slightly delayed type.

The patient's height and weight were almost the mean until the age of 11. At annual X-ray examinations, bone ages were delayed only one year as compared with his chronological age, and the patient's growth spurt started at about the age of 13. His adolescence was of the slightly delayed type. At the age of 15, his height was 167 cm, and his weight was 57 kg (Fig. 1).

Discussion

The mental development of children with CH has been improved as a result of early detection by neonatal screening and an appropriate therapy (5, 6). Newborns classified false positive at CH screening have a very high risk of subclinical hypothyroidism in infancy and early childhood (7).

Fig. 2 Clinical course until the age of 13. The dosage of thyroid hormone was gradually increased as he grew and the maximum dose was 110 $\mu\text{g/day}$. Serum levels of TSH were within the normal range. At the age of 13 yr and 4 mo, the serum level of TSH dropped to an undetectable level.

Nevertheless, it is difficult to decide whether a case should be treated or not in cases such as transient hypothyroidism, transient hyperthyrotropinemia, mild congenital hypothyroidism, and persistent hyperthyrotropinemia at the early phase of consultation (8).

The present case was considered subclinical CH with high TSH and normal T_4 levels. Thus thyroid hormone replacement therapy was started at the age of 34 d. The patient's serum levels of TSH were sometimes high, and as he grew, the dosage of thyroid hormone was escalated to a maximum dose of 110 $\mu\text{g/day}$ until the age of 11. His clinical course was consistent with that of permanent CH till the age of 13, and it is speculated that he

suffered from an iodine organification defect at that time.

Van der Gaag *et al.* found transplacental passage of maternal immunoglobulins may play a part in the pathogenesis of CH (9). Kato *et al.* described two cases of CH detected by screening whose sera contained high levels of antibodies in early childhood, and concluded that the antibodies were not derived from maternal immunoglobulins but produced on their own (10).

Therefore we hypothesize that in the present case hypothyroidism was transient due to immaturity of iodine organification in the thyroid gland as Nose *et al.* described previously (11), and that afterwards hyperthyroidism developed due to

Fig. 3 Clinical course after the age of 13. The initial dosage of methimazole (MMI) was 20 mg/day. One month after the start of therapy, the serum level of free T₄ was normalized. After two months of therapy, the serum level of TSH had risen to a detectable level.

an autoimmune disease, and was diagnosed with the results of serum TRAb and the thyroid scan. It is also possible that the patient had several clones of antibodies against thyroid from his early infancy. Although the patient's mother had no thyroid disease and his antibodies were negative in early childhood, a clonal change in his antibodies might have happened and their binding properties could have been altered from the blocking type to the stimulating type (4, 12).

We could not find a similar case in the literature. Further analysis of thyroid function is apparently necessary to assign the immunological basis of this case and additional follow-up data should be accumulated during the treatment course of this patient.

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