Non-autoimmune neonatal hyperthyroidism due to A633G mutation in the thyrotropin receptor gene

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Introduction

Congenital hyperthyroidism is a rare disease. In most patients with congenital hyperthyroidism are autoimmune forms caused by maternal thyroid-stimulating antibodies. In contrast to autoimmune hyperthyroidism that is transient, non-autoimmune form of congenital hyperthyroidism is persistent and results from activating germline mutations in the thyrotropin receptor (TSHR) gene. We report the case of a Korean male infant with severe nonautoimmune neonatal hyperthyroidism due to germline TSHR mutation (A633G).

Case report

- A 24-day-old male
- Chief complaint: persistent tachycardia
- Birth history: delivered by emergency Caesarian section at 33 weeks of gestational age because of fetal tachycardia and premature rupture of membranes
- Maternal history: non-specific
- Physical examination: tachycardia without murmur
- Echocardiography and electrocariography: sinus tachycardia
- Thyroid function tests: T3 10.52 ng/mL (0.78-1.82), free T4 3.98 ng/dL (0.85-1.86), and TSH 0.05 mIU/L (0.17-4.05)
- Antibodies to TSHR, thyroid peroxidase (TPO) and thyroglobulin (TG): negative
- Thyroid ultrasonography: increased vascularity and 2 mm sized hypoechoic nodule in right thyroid
- Thyroid scan: diffusely increased uptake and goiter
- Direct sequencing of TSHR gene: a heterozygous C to A transition leading to a substitution of aspartic acid for glutamic acid at codon 633 in exon 10 (Fig. 1). Molecular analysis of his parents TSHR gene revealed no mutation.

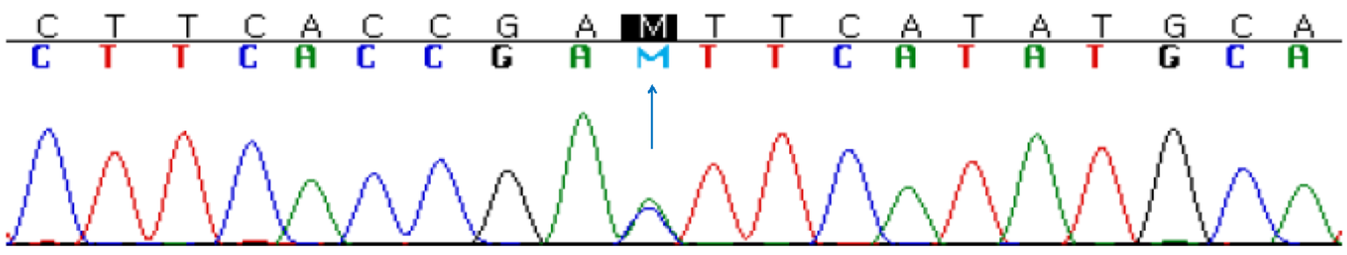

Fig. 1. Patient's TSHR gene sequencing.

- Progress: He was started on propylthiouracil (PTU, 5 mg/kg) and propranolol. It was difficult to control hyperthyroidism, we had to increase the dose of PTU (7.5 mg/kg). At the age of 3 months, he showed craniosynostosis and hydrocephalus. He underwent ventriculoperitoneal shunt operation. After 6 months of PTU treatment, thyroid function tests showed euthyroid state and tachycardia was resolved. PTU was changed to methimazole. After reducing the dose of methimazole(0.3 mg/kg), hyperthyroidism was relapsed. We increased the dose of methimazole again (1.0 mg/kg). Now, we consider the thyroidectomy or radioiodine treatment.
- At 12 months of age: his height was 50-75th percentile and weight was 20-50th percentile. Bone age was advanced (2 years and 8 months of age).

Summary

This is the first report of a sporadic non-autoimmune congenital hyperthyroidism due to Asp633Glu mutation in the TSHR gene. Non-autoimmune congenital hyperthyroidism is characterized by frequent relapses after antithyroid agents treatment. Thyroid ablation by total thyroidectomy or radiatherapy is the only treatment can prevent relapses of the hyperthyroidism.

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