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 electrocardiography: 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.

![Thyroid gene sequencing](image)

• 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 radiiodine 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 radiodine therapy is the only treatment can prevent relapses of the hyperthyroidism.