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Case report

TSHRV656F Activating Variant of the Thyroid Stimulating Hormone Receptor Gene in Neonatal Onset Hyperthyroidism: A Case Review

Short Title: Neonatal Hyperthyroidism by TSHRV656F mutation

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What is already known about this topic?
Neonatal hyperthyroidism is a rare condition and is most frequently caused by the transplacental transmission of TRsAB from a mother with Graves' disease. Activating variants of the *TSHR* gene are rare causes of neonatal hyperthyroidism which play significant role in the etiology of familial (AD) and sporadic non-autoimmune hyperthyroidism (NAH).

What this study adds?
We present a case of neonatal onset congenital NAH with a sporadic germline activating V656F variant in *TSHR* gene. This variant was described in the literature as a somatic variant in children and adults with toxic thyroid nodule(s) that resulted in the structural activation of the TSH receptor. This study is the first case review that highlights the relationship between this variant and neonatal onset non-autoimmune hyperthyroidism.

ABSTRACT
Activating variant of the thyroid stimulating hormone receptor (TSHR) gene is one of the rare causes of neonatal hyperthyroidism. This disorder may occur as a result of an autosomal dominant (AD) inheritance or sporadically through de novo variants. Here we present a case of neonatal onset congenital non-autoimmune hyperthyroidism (NAH) with a sporadic germline activating TSHRV656F variant. A female infant with tachycardia, who was transferred due to hyperthyroidism in the first week of life, displayed no other symptoms or signs; the patient's mother did not have Graves' disease, and TSHR stimulating antibodies (TRsAB) were not present in the mother or baby. Imaging showed thyroid gland hyperplasia and left ventricular hypertrophy, the patient was subsequently put on methimazole treatment. After 6 months of undergoing treatment, a heterozygous p.Val656Phe (V656F) (c.1966G>T) variant was detected on exon 10 of the TSHR gene. The variant was not identified in the mother and father, so the case was determined to be sporadic. In conclusion, although the literature describes V656F variant as a somatic variant in children and adults with toxic thyroid nodule(s) that results in the structural activation of the TSH receptor, it was determined that no cases of neonatal hyperthyroidism due to TSHRV656F variant were reported. This study is the first case review that highlights the relationship between TSHRV656F variant and neonatal onset non-autoimmune hyperthyroidism.
Keywords: neonatal hyperthyroidism, activating variant of *TSHR* gene, non-autoimmune hyperthyroidism

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INTRODUCTION

Hyperthyroidism in children is a rare heterogeneous condition characterized by an excessive production of thyroid hormone (1). Approximately 1% of childhood thyrotoxicosis cases emerge in the neonatal period. Neonatal hyperthyroidism, which has an estimated prevalence of 1/50,000, is primarily caused by temporary hyperthyroidism due to maternal Graves' disease and is characterized by the presence of thyroid receptor stimulating antibodies (TRsAB) that have been passed on to the newborn by the mother (2,3). Autoimmune congenital hyperthyroidism continues for nearly four months following birth and is alleviated when the maternal TRsAB is gradually eliminated from the infant's blood (3). Persistent neonatal cases of hyperthyroidism in which no antibodies are detected may be related to less common non-autoimmune genetic etiologies such as activating variants in the TSHR gene, somatic activating variants of the GNAS gene which encodes the stimulant alpha sub-unit of the guanine nucleotide binding protein (as is the case in MAS), and less frequently through variants in the Thyroid Receptor β gene (3,4). McCune Albright Syndrome is an uncommon etiology of neonatal hyperthyroidism, and is characterized by additional findings including cafe au lait macules on the skin, skeletal deformities caused by fibrous dysplasia, and signs associated with hormonal hyperfunction (cushing syndrome, peripheral precocious puberty, etc) (5). In the literature, there have been case reports of individuals diagnosed with thyroid hormone resistance due to variants in the

Thyroid Receptor β gene, leading to neonatal hyperthyroidism symptoms; however, unlike the others, suppression of serum TSH was not observed in these patients (6,7).
In the literature, activating TSHR gene variants have been frequently reported in the genetic analysis of children and adults with toxic thyroid nodule(s) (8-11), and less commonly in cases of neonatal hyperthyroidism (12,13).
In this study, we present a case of neonatal onset congenital non-autoimmune hyperthyroidism (NAH) with a sporadic germline activating TSHRV656F variant, and whose family history is negative for non-autoimmune hyperthyroidism.

CASE

A female patient is the third live born from the fourth pregnancy of a 27-year-old mother, born at term through normal vaginal birth weighing 3110 g. The patient exhibited tachycardia on the third day. The patient's family history was negative for thyroid disease; however, the mother was observed to have goiter during evaluation. Physical examination revealed body weight to be 3600g (50-75p), height 48cm (10-25p), head circumference 35cm (25-50p), rhythmic heart rate 160-170/min. Other than mild tachycardia, no signs of pathology were observed, cafe au lait macules were not present on the skin. Laboratory tests revealed a free thyroxine (fT4) level of 3.41 ng/dL (0.93-1.7), and thyroid stimulating hormone (TSH) level of 0.005 mIU/mL (0.35-4.94). Laboratory analysis at 7 days of age showed the serum level of free triiodothyronine (fT3) as 12.54 pg/mL (1.8-4.6), fT4 level 3.22ng/dL (0.83-1.76), and TSH level <0.01 mIU/L (1.78-12.6) consistent with hyperthyroidism. While anti-thyroid peroxidase (anti-TPO) antibody was found positive in the serum, anti-thyroglobulin (anti-TG) and TSH receptor antibodies (TRAB) were not detected. Thyroid ultrasonography (US) revealed diffuse hyperplasia of the thyroid gland. Echocardiogram showed mild hypertrophy of the left ventricle. The thyroid function tests of the mother were reported as euthyroid; anti-TPO and anti-TG antibodies were present in the serum, TRAB was not.
At seven days of age, the patient was put on treatment with 0.5 mg/kg/day Methimazole (in two doses) and 2mg/kg/day Propranolol (in two doses). On the 8th day of treatment, Methimazole treatment was reduced and eventually discontinued due to low fT4 levels. However, on the 5th day following medical discontinuation, thyroid function tests revealed hyperthyroidism and the patient was put back on Methimazole. Based on the results of thyroid function tests, the dose of treatment was adjusted between 0.15-0.75 mg/kg/day, and the patient had maintained a euthyroid state. Propranolol treatment was discontinued as the patient's tachycardia had resolved.
The patient had tested negative for TRAB from the onset of disease, anti-TPO antibodies had receded, and the patient required more than 6 months of anti-thyroid treatment; for these reasons, a prediagnosis of NAH was considered. The patient did not demonstrate any additional signs of MAS, and a TSHR p.Val656Phe (c.1966G>T) heterozygous variant was detected on exon 10 of the TSHR gene. The case was confirmed to be sporadic as the same variant was not detected in the mother and father (Figure 1).
During follow-up of methimazole treatment; the patient's physical examination showed normal sized thyroid glands, normal growth and development, and two periodic thyroid USG evaluations gave normal results. During the last assessment at 25 months of chronological age, the patient's height was 85 cm (10-25p), which was in conformity with her genetic target height, and body weight was 11.1 kg (10-25p). Neuromotor development was proper with respect to chronological age. The patient was still continuing Methimazole treatment (0.45 mg/kg/day) and maintained a euthyroid state.

DISCUSSION

Here we present a case of neonatal onset congenital non-autoimmune hyperthyroidism (NAH) with a sporadic germline activating TSHRV656F variant. When hyperthyroidism is detected in a newborn, autoimmune reasons must initially be considered and the baby as well as the mother should be assessed for TRsAB. If no autoimmune reasons can be identified in persistent cases of neonatal hyperthyroidism, genetic etiologies should be considered (3).
Since our patient had a persistent NAH and there were no additional findings suggestive of MAS, genetic analysis was conducted initially for *TSHR* activating variants, and a heterozygous sporadic activating V656F(Val656Phe) variant was detected on the *TSHR* gene. Activating germline variants of the *TSHR* gene that display an AD inheritance pattern lead to familial or hereditary NAH (FNAH); on the other hand, de novo variants cause sporadic NAH (SNAH), as is the case in our patient. Although uncommon, somatic variants of the *TSHR* gene can also lead to autonomic thyroid adenomas in children (14).
Data in the literature regarding activating *TSHR* variants and their clinical characteristics are accessible on a periodically updated database formed in 1999 (15). In the literature, there have been limited cases of SNAH in which symptoms were present during the neonatal period (12,13). The variant detected in our case was first observed in 1997 by Führer et al. in a patient with toxic thyroid nodule (8). In their study, Wonerow et al. confirmed this variant to be an activating point variant of the TSHR gene (9). In subsequent years, this variant was observed in some child and adult patients with toxic thyroid nodule(s) (8-11,16,17). However, after a thorough review of the literature, we did not find any reports of the variant in neonatal cases of hyperthyroidism to date. In comparison to FNAH, cases of SNAH tend to show symptoms at an earlier age and exhibit more severe clinical manifestations. However, the signs may be affected by genetic, epigenetic, and environmental factors as well as the in vitro activity of TSHR gene variants. Akcurin and colleagues reported 3 cases of the same variant from the same family in which FNAH emerged at different ages. One of the siblings had symptoms during infancy and was diagnosed with hyperthyroidism at age 3.5, the other was diagnosed at 12 days old, and their father was diagnosed with toxic multinoduler goiter at 36 years old (18). To be concise, the phenotype-genotype relationship of the disease is not clear.
Congenital NAH can show clinical signs even in the fetus; this includes tachycardia, arrhythmia, intrauterine growth restriction, and premature birth (12). Our patient was born term with a normal birth weight. In the first week of the neonatal period, tachycardia was observed in the patient's physical examination. Imaging displayed signs of potential intrauterine involvement, including diffuse hyperplasia of the thyroid gland and mild left ventricular hypertrophy. After the neonatal period, NAH can manifest in babies as tachycardia, growth retardation, accelerated linear growth, advanced bone age, craniosynostosis, restlessness and/or delay in development (14). In our case, these manifestations were prevented in infancy by ensuring a euthyroid state through ATM. NAH typically causes diffuse enlarged goiter in childhood, and progresses to multinodular goiter in older ages. An important diagnostic criterion for NAH is absence of ophtalmopathy.. Unlike Graves'

disease, serological testing shows no anti-thyrotropin receptor antibodies, and histopathological examination of thyroid tissue is not characteristic of mononuclear cell infiltration; autoimmune markers are not observed in immunohistological analysis (19).

The treatment for hereditary and persistent sporadic NAH differs from that of autoimmune hyperthyroidism in which anti-thyroid medication (ATM) is temporarily (3-4 months) used (3). Congenital NAH that is caused by activating variants of the *TSHR* gene presents with persistent and severe hyperthyroidism manifestations; for this reason, ATM may be initially used, but curative approaches such as surgery or Radioactive iodine (RAI) ablation are required (20). Otherwise, the patient may experience relapses of hyperthyroidism following discontinuation of ATM. Relapses may even be observed in cases of incomplete ablation (subtotal thyroidectomy or a RAI dose that is non-ablative). Remission is observed in nearly 50% of patients one year after ATM. In SNAH, the recovery time of the pituitary-thyroid feedback axis cannot be predicted, and TSH may remain suppressed for more than one year following birth. Because FNAH and SNAH are uncommon, well characterized case series have presented valuable information regarding the best treatment methods and various therapeutic modalities. In our case, euthyroidism was quickly attained through ATM, and curative treatment was planned for future years.

CONCLUSION

We have reported the first case of neonatal hyperthyroidism associated with a sporadic activating V656F variant of the *TSHR* gene. Sporadic de novo activating variants in TSHR gene can cause a severe case of hyperthyroidism in the neonatal period. As in our case, in patients who present with persistent NAH with early onset diffuse goiter, and who have no family history or additional systemic involvement, sporadic activating *TSHR* gene variants should be considered; genetic analysis should be planned. Genetic diagnosis is also a guide for treatment because curative treatment is ultimately required during follow-up in these patients.

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Figure 1.