Toxic Thyroid Adenoma Presenting as Hypokalemic Periodic Paralysis

TETSUYA TAGAMI, TAKESHI USUI, AKIRA SHIMATSU AND MITSUHIDE NARUSE

Clinical Research Institute, Division of Endocrinology and Metabolism, Kyoto Medical Center, National Hospital Organization, Kyoto 612-8555, Japan

Abstract. Toxic thyroid adenoma presenting as hypokalemic periodic paralysis is extraordinarily rare. We describe a 26-year-old Japanese man who suffered from acute and painful muscle weakness of extremity in the morning. Physical examination showed a left anterior neck mass and laboratory tests revealed hypokalemia during his paralysis, and thyrotoxicosis. Neck sonogram showed a solitary nodule in the left lobe of the thyroid. Thyroid scintigraphy revealed a hot nodule of the tumor region with suppressed uptake in the other thyroid area. The tumor was surgically removed and his paralytic attack ceased. No somatic mutation of TSH receptor was found in his thyroid adenoma and no known genetic mutations of ionic channel genes, such as calcium (CACN1S), sodium (SCN4A) and potassium (KCNE3), were found.

Although thyrotoxic periodic paralysis is usually accompanied with Graves’ disease, thyrotoxicosis of other conditions including Plummer’s disease should be considered.

Key words: Plummer’s disease, Toxic thyroid adenoma, Autonomous functioning adenoma, Thyrotoxic hypokalemic periodic paralysis, Thyrotoxicosis

THYROTOXIC periodic paralysis (TPP) is a sporadic disorder characterized by episodic attacks of muscle weakness concomitant with hypokalemia and thyrotoxicosis. The clinical features of TPP are similar to familial hypokalemic periodic paralysis. Some of the precipitating factors for these conditions include heavy carbohydrate-rich meals, glucose or insulin perfusion, and acute stress. Familial periodic paralysis presents autosomal dominant heredity and an ion-channel abnormality. Mutations of the calcium channel alpha-1 subunit (Ca,1.1: CACN1AS; R528H, R1239H, R1239G), the sodium channel alpha subunit (Na,1.4: SCN4A; R669H, R672G, R672H) and the skeletal muscle voltage-gated potassium channel (K,3.4: KCNE3; R83H) have been reported [1–5]. Although the pathogenesis of TPP remains unclear, TTP does not recur once the patient is euthyroid. The majority of thyrotoxic patients associated with TPP is due to Graves’ disease, while other conditions have been uncommonly implicated.

Toxic thyroid adenoma (Plummer’s disease) is a condition where thyrocytes function and produce thyroid hormones independently of thyrotropin (TSH) and in the absence of TSH-receptor stimulating antibodies. The autonomous secretion of thyroid hormones leads to TSH suppression and silence in the nonautonomous thyroid tissue, and can ultimately result in thyrotoxicosis [6, 7]. Several somatic point mutations in the TSHR gene [8–10] and in the G protein genes [11] have been reported, that lead to a state of constitutive activation of the TSH receptor and result in the autonomic growth of adenoma(s).

We report here a case of TPP caused by a toxic thyroid adenoma. Plummer’s disease should be kept in the differential diagnosis in any TPP patients with nodular goiter to avoid delaying diagnosis and management.
Case Report

A 26-year-old man consulted a practitioner because of acute and painful muscle weakness of extremity for the past 10 days. His symptom was severer in the morning and he could not rise easily. He was also aware of palpitation, tremor and hyperhidrosis. Nodular goiter was indicated and thyroid function tests revealed elevated free T4 and suppressed TSH. Under a prescription of β-blocker, he was referred to the thyroid clinic of Kyoto Medical Center. His height was 174 cm and body weight was 69 kg. Physical examination revealed a blood pressure of 122/60 mmHg and a regular pulse of 80 per minute. He had fine finger tremor and his skin was wet. A nodule, 4 cm in diameter, was palpated in the left anterior neck. Muscle strength was unremarkable at the time. Serum potassium was 4.2 mEq/l and creatine kinase was 94 IU/l. Thyroid function tests revealed free T4 = 2.4 ng/dl (normal, 1.0–1.8), free T3 = 7.1 pg/ml (normal, 2.3–4.0), TSH<0.01 µU/ml. There was no family history of neuromuscular or endocrine abnormality. A few days later, he had an emergency visit because of acute paralysis of extremity and the paralysis was remitted with a potassium infusion. Serum potassium was 2.0 mEq/l and creatine kinase was 154 IU/l at the time of the visit. Anti-TSH receptor autoantibodies and anti-thyroid autoantibodies (anti-thyroglobulin and anti-thyroid peroxidase antibodies) were all negative. Ultrasonography showed a nodule of iso-echogenecity with a low-echogenecity region inside in the left lobe of the thyroid (Fig. 1). Fine needle aspiration biopsy revealed thyroid adenoma with cystic degeneration inside the nodule. Thyroid scan using $^{123}$I revealed a hot nodule of the tumor region and suppressed uptake in the other thyroid area, with a 24-hour uptake of 31% (Fig. 2). After the diagnosis of a hyperfunctioning thyroid adenoma, the tumor was surgically removed. He became euthyroid and no recurrent paralytic attack has been observed to date.

![Fig. 1. Ultrasonography of the thyroid shows normal right lobe and enlargement of the left lobe, which is occupied with a solitary nodule of iso-echogenecity in the ambient and low-echogenecity inside.](image1)

![Fig. 2. Thyroid scan using $^{123}$I shows a hot nodule of the tumor region and suppressed uptake in the other thyroid area, with a 24-hour uptake of 31%.](image2)
Materials and Methods

Genetic gene analysis

Informed consent was obtained for the genetic analysis of ionic channel genes from the patient and blood samples were taken. Genomic DNA was extracted from peripheral blood leukocytes using an EZ1 DNA Blood 200 µl kit (Qiagen, Hilden, Germany). The specific amplifications for the calcium channel alpha-1 subunit (CACN1AS), the sodium channel alpha subunit (SCN4A) and the skeletal muscle voltage-gated potassium channel (KCNE3) were performed using four sets of primers as shown in Table 1. Polymerase chain reaction (PCR) was performed in a final volume of 25 µl containing 12.5 µl of 2 × GC buffer 1 (Takara, Shiga, Japan), 200 nM of each dNTP, 1 mM of each primer, 10 ng genomic DNA, and 5 U of LA Taq polymerase (Takara). Amplifications were carried out at 95°C for 0.5 min, 55°C for 1 min, and 72°C for 1 min for 35 cycles. PCR products were purified using QIAquick Gel Extraction kit (Qiagen), and subsequently sequenced using the primers used for PCR. Sequencing was performed using a BigDye Terminator Cycle Sequencing kit and an ABI PRISM 310 Genetic Analyzer (Applied Biosystems, Foster City, CA).

RT-PCR

Informed consent was obtained for the somatic gene analysis of the thyroid tumor from the patient and the surgically removed tissue was kept in RNAlater solution (Ambion, Austin, TX) until RNA extraction. Total RNA was isolated using ISOGEN (Nippon Gene, Tokyo, Japan), and was reverse-transcribed with the AMV RNA PCR kit (Takara) in the presence of oligo dT as a primer. Subsequently, PCR was performed for TSH receptor using the primers shown in Table 1. Amplifications were carried out at 95°C for 0.5 min, 60°C for 1 min, and 72°C for 1 min for 35 cycles. PCR products were purified using QIAquick Gel Extraction kit (Qiagen), and subsequently sequenced using the primers for TSH receptor.

Results

Ionic channel analysis

Genetic gene analysis was performed on the reported regions of ionic channel genes. No germline mutation was observed in the Ca\textsubscript{v}1.1 (R528, R1239), Na\textsubscript{v}1.4 (R669, R672) or K\textsubscript{v}3.4 (R83) genes. Polymorphisms in nucleotides 1551 and 1564 in the exon 11 of Ca\textsubscript{v}1.1, those are near to R528 at nucleotide 1583, were also sequenced [12]. The genotype of 1551C/T was TT and that of 1564C/T was CC [39]. The polymorphism, 290T/C of K\textsubscript{v}3.4 was CC [14].

TSHR analysis

RT-PCR was performed using the resected tissue of adenoma. The PCR products were purified and sequenced. No TSH-receptor somatic mutation was observed in the cDNA derived from the tumor tissue.

Discussion

The case we report here had toxic thyroid adenoma

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primers</th>
</tr>
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<tbody>
<tr>
<td>Ca\textsubscript{v}1.1 (CACN1AS) for R528</td>
<td>S ATGTCTATCTTCAACCGCTTC</td>
</tr>
<tr>
<td></td>
<td>A TCCCATGAGCCGGATGCAG</td>
</tr>
<tr>
<td>Ca\textsubscript{v}1.1 (CACN1AS) for R1239</td>
<td>S TGACCCAGATGAGAGTGCC</td>
</tr>
<tr>
<td></td>
<td>A GGTAGGCGCTGGAAGGAGCTTG</td>
</tr>
<tr>
<td>Na\textsubscript{v}1.4 (SCN4A)</td>
<td>S CTCTGTGACAGGCGGCTCCATG</td>
</tr>
<tr>
<td></td>
<td>A TCTTACCCACCCACCCATCC</td>
</tr>
<tr>
<td>K\textsubscript{v}3.4 (KCNE3)</td>
<td>S CCTTCTCTTTCTTTTCTTGGCCAC</td>
</tr>
<tr>
<td></td>
<td>A TTACAGATAGGGGACTCATGAGAGGC</td>
</tr>
<tr>
<td>TSH receptor for mRNA</td>
<td>S TAGCCCGAGTCCTCCCCTGAAA</td>
</tr>
<tr>
<td></td>
<td>A TGTAGTGTGAGTAGTGTGAAAC</td>
</tr>
</tbody>
</table>

S, sense; A, antisense.
complicated with TPP. His chief complaint was muscle weakness, and hyperthyroidism with nodular goiter was detected upon examination. TPP is most usually associated with Graves’ disease probably because TPP is common in males of Asian descent where hyperthyroidism is mainly due to Graves’ disease. Accordingly, toxic thyroid adenoma presenting with hypokalemic periodic paralysis is extraordinarily rare in the world [15]. Other conditions such as toxic nodular goiter [16], thyroiditis [17], TSH-secreting pituitary tumor [18, 19], ingestion of T4 [20], and inadvertent iodine excess [21], and radiation thyroiditis with Graves’ disease [22] have been reported.

The precise pathogenesis of TPP remains unclear but hypokalemia is the consequence of a rapid and massive shift of potassium from the extracellular into the intracellular compartment, related to increased sodium-potassium-adenosine triphosphate (Na/K-ATPase) pump activity [23–25]. Patients with TTP have significantly higher Na/K-ATPase pump number and activity than thyrotoxic patients without TTP, and the activity returns to control level when their thyroid function is controlled. The potassium shift into the intracellular compartment is mainly the flux into muscles. Thyroid hormone, β-adrenergic catecholamine and insulin can increase Na/K-ATPase pump activity in skeletal muscles, liver or kidneys [26–31]. Thyroid hormone-responsive elements are present in the upstream region of the α1-, α2-, β1-, β2- and β4-Na/K-ATPase subunit genes, those are all expressed in skeletal muscles [32, 33], and T3 can increase Na/K-ATPase pump activity through both transcriptional and posttranscriptional mechanisms [34, 35]. Clinically, TPP is precipitated by oral glucose challenge with an exaggerated insulin response and is aborted or prevented by nonselective β-adrenergic blockers. However, no mutations were identified in the S′ upstream region and the coding region of these five Na/K-ATPase subunit genes [36] and no association between TPP and the SNPs of these five genes [37]. Similarly, the SNPs in the β2-adrenergic receptor gene were not associated with TPP [38].

Since the clinical features of TPP are very similar to the familial hypokalemic periodic paralysis (FHPP) and the mutations in the ionic channel genes have been reported in FHPP, the search for mutations has been performed in TPP. The mutations found in FHPP so far were on the L-type calcium channel alpha-1 subunit (Ca,1.1: CACN1AS; R528H, R1239H, R1239G), the sodium channel alpha subunit (Na,1.4: SCN4A; R669H, R672G, R672H) and the skeletal muscle voltage-gated potassium channel (K,3.4: KCNE3; R83H) [1–5]. The mutation of the Na,1.4 gene may increase sodium permeability of the muscle cellular membrane and decrease resting membrane potential, resulting in paralysis [4]. The mutation of the K,3.4 gene may prevent the extracellular shift of potassium, resulting in hypokalemia [5]. The mechanism of the mutation in the Ca,1.1 gene to induce hypokalemia and paralysis is unclear. Although no mutations were found in the hot spots of FHPP in the Ca,1.1 gene [12, 39–43], single-nucleotide polymorphisms (SNPs) of Ca,1.1 were associated in patients with TTP [12, 13] and a positional implication with the TRE has been discussed because these SNPs lie at or near the TRE half site sequence. Similarly, although most of studies failed to detect mutations of the Na,1.4 and K,3.4 genes [13, 14, 41, 43], one pediatric Caucasian patient with TTP had an R672G mutation of the Na,1.4 and one TPP patient of Portuguese descent had an R83H mutation in the K,3.4 gene. However, the R672G mutation of the Na,1.4 was also carried by the family members who had hypokalemic paralysis without thyrotoxicosis and the patient with R83H mutation in the K,3.4 seems to have been also reported as FHPP [14, 44]. In addition, the R83H mutation in the K,3.4 gene was present at frequency of 1–5% in the Caucasian population [45] while it was not detected in the Asian population [14].

Since it has been reported that somatic mutations in the thyrotopin receptor (TSHR) gene cause hyperfunctioning thyroid adenomas [8], numerous mutations in the TSHR gene were found to be capable of inducing constitutive activation of the cAMP regulatory cascade [46–51]. The similar mutations were also found in Japanese population [52, 53] and the frequency was 70%. No mutation in the TSHR gene of the toxic adenoma was found in our patients.

We reported a rare case of TPP associated with toxic adenoma and examined several ionic channel genes that are reported in FHPP, and somatic TSH receptor mutation. No mutations were found at hot spots in the Ca,1.1, Na,1.4 and K,3.4 genes and no somatic mutations in the toxic adenoma were found in the TSHR gene. The genetic background of TPP may be different from that of FHPP, taking into account the literature reported so far. Further investigation is necessary to elucidate the pathogenesis of TTP. In conclusion, TPP is not always associated with Graves’ disease.
Acknowledgments

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References


identification of additional mutations activating both the cyclic adenosine 30, 50-monophosphate and inositol phosphate-Ca\textsuperscript{2+} cascades. *Mol Endocrinol* 9: 725–733.


