CASE REPORT

Thyrotoxic Periodic Paralysis with Graves’ Disease Leading to the Discovery of a Hidden Nonclassic 11β Hydroxylase Deficiency

Jin Hwa Kim¹, Geon Park², Sang Yong Kim¹ and Hak Yeon Bae¹

Abstract

11β hydroxylase deficiency (OHD) is one of the main causes of congenital adrenal hyperplasia. There have been only a few reported cases of nonclassic 11β OHD, a milder form of the disease. It is difficult to detect occult nonclassic 11β OHD because patients present with no or mild symptoms. We herein present a case of thyrotoxic periodic paralysis (TPP) with Graves’ disease leading to the discovery of a hidden nonclassic 11β OHD. In this case, increased levels of thyroid hormone seem to have induced symptoms of occult nonclassic 11β OHD and aggravated TPP.

Key words: nonclassic 11β hydroxylase deficiency, congenital adrenal hyperplasia, thyrotoxic periodic paralysis


Introduction

11β hydroxylase deficiency (OHD) is one of the main causes of congenital adrenal hyperplasia (CAH) (1). Nonclassic 11β OHD is a milder form than the classic form regarding the clinical manifestations, which are caused by the partially impaired function of CYP11B1. It is difficult to detect occult nonclassic 11β OHD because patients present with no or mild symptoms. Reported cases of nonclassic 11β OHD are rare (2).

Thyroid hormones increase the turnover of cortisol. Thyroxine replacement without steroid replacement cause an adrenal crisis in patients with a combined condition of hypothyroidism and adrenocortical insufficiency. Increased levels of thyroid hormones can induce symptoms of occult nonclassic congenital adrenal hyperplasia, which can lead to adrenal crisis (3).

We herein describe an instructive case leading to the discovery of previously unrecognized nonclassic 11β OHD in a patient with thyrotoxic periodic paralysis (TPP) with Grave’ disease.

Case Report

A 23-year-old man presented with paralysis of both lower extremities. One day before admission, he had climbed a mountain and overate at dinner, then at 5 AM on the day of admission, he experienced proximal muscle weakness. He had no significant past medical or family history. He was not taking medications. On admission, his temperature was 36.5°C, his pulse was 118 beats per minute and his blood pressure was 170/100 mmHg. A physical examination revealed paralysis of both legs and a slightly enlarged palpable thyroid gland. There were no sensory deficits or respiratory difficulties.

The laboratory data obtained on admission showed the following levels of serum electrolytes: Na: 141 mEq/L, K: 1.9 mEq/L, Cl: 109 mEq/L, calcium: 9.24 mg/dL and phosphorus: 3.9 mg/dL. An arterial blood gas analysis performed on room air demonstrated a pH of 7.429, a PaO₂ of 98.9 mmHg, a PaCO₂ of 39.3 mmHg and a HCO₃ of 26.5 mmol/L. The patient’s urinary potassium excretion decreased to 9.1 mEq/L (normal: 25-125 mEq/L). Thyroid function tests

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an undisclosed adrenal gland causing secondary hypertension in TPP patients. We wanted to confirm whether there was a clinical picture of thyrotoxicosis. The patient was treated with potassium replacement, methimazole and propranolol during hospitalization. His blood pressure was sustained at 140/90 mmHg. Thereafter, we did not administer glucocorticoid therapy, and the patient was discharged. Seventeen months later, an ACTH stimulation test was performed to assess the cortisol level at euthyroid status. The levels of basal and ACTH-stimulated cortisol were found to have improved (Table). The ACTH stimulation test was found to have decreased at 216 pg/mL. We could not assess the levels of adrenal steroid precursors because the patient refused to undergo any further evaluations. He had no symptoms and his blood pressure was sustained below 140/90 mmHg. The patient is receiving follow-up at the outpatient clinic.

Table. The Levels of ACTH-stimulated Adrenal Steroid Precursors and Cortisol on Admission and during Euthyroidism

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>After ACTH stimulation</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>17α-hydroxypregnenolone (ng/mL)</td>
<td>7.81</td>
<td>19.30</td>
<td>0.1-4.0</td>
</tr>
<tr>
<td>17α-hydroxyprogesterone (ng/mL)</td>
<td>47.6</td>
<td>272</td>
<td>0.6-3.4</td>
</tr>
<tr>
<td>11-deoxycortisol (ng/dL)</td>
<td>135</td>
<td>739</td>
<td>0-120</td>
</tr>
<tr>
<td>Cortisol (μg/dL)</td>
<td>1.2</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>At euthyroidism (17 month later)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol (μg/dL)</td>
<td>10.2</td>
<td>10.6</td>
<td></td>
</tr>
</tbody>
</table>

 disclosed elevated serum levels of free T4 at 3.48 ng/dL (normal: 0.7-1.8 ng/dL) and T3 at 530.2 ng/dL (normal: 60-190 ng/dL) with a low thyroid stimulating hormone (TSH) level at 0.01 μIU/mL (normal: 0.25-4 μIU/mL), which confirmed a clinical picture of thyrotoxicosis. The patient was positive for anti-microsome antibodies at a titer of 2,682 UI/mL and TSH R antibodies at a level of 25.4% (normal: 0-15). His blood cell counts and liver function tests were normal. Ultrasonography (US) of the thyroid gland showed a diffuse goiter.

A diagnosis of TPP with Graves’ disease was made, and the patient was treated with potassium replacement, methimazole (20 mg) and propranolol (60 mg).

However, the patient exhibited prominent diastolic hypertension and hypokalemia compared to that observed in general TPP patients. We wanted to confirm whether there was an undisclosed adrenal gland causing secondary hypertension. On abdominal computed tomography (CT), both adrenal glands showed hyperplasia (Fig. 1). Therefore, we conducted a more detailed investigation of the patient’s past history. The patient’s history revealed that his growth had stopped at around the age of 15 years, and pubic hair development started at around the age of 10 years. His height was 171 cm and his weight was 71.3 kg. He did not have ambiguous external genitalia.

Laboratory assessments showed elevated levels of adrenocorticotropic hormone (ACTH, 357 pg/mL), androstenedione (939 ng/dL, normal: 30-263 ng/dL) and urinary 17-ketosteroid (61.3 mg/day, normal 0-25 mg/day). An ACTH stimulation test was performed to assess the levels of adrenal steroidogenic enzymes. The basal and ACTH-stimulated 11-deoxycortisol levels were elevated at 135 and 739 ng/dL, respectively (normal: 0-120 ng/dL). The levels of ACTH-stimulated adrenal steroid precursors and cortisol are summarized in Table.

Therefore, we confirmed the coexistence of nonclassic 11β OHD.

To determine the presence of molecular genetic variations, we performed polymerase chain reaction (PCR)-direct sequencing of the CYP11B1 gene. Genomic DNA was extracted from venous blood using a QIAamp DNA Blood mini kit (Qiagen, Valencia, CA). We found two hypofunctional genetic polymorphisms of the CYP11B1 gene, including c.128 G>A and c.595+12 G>A (Fig. 2).

Figure 1. Abdominal computed tomography showing hyperplasia of both adrenal glands (arrows).

Figure 2. Two genetic polymorphisms in exon 1 and intron 3 of the CYP11B1 gene. (A): Exon 1 sequence. A c.128G>A substitution was revealed. (B): Intron 3 sequence. A c.595+12G>A substitution was revealed.
Discussion

CAH is caused by several partial impairments of adrenal steroidogenesis that affect cortisol biosynthesis (4). Steroid 11β OHD is the second most common cause of CAH and accounts for 5-8% of cases (5). 11β OHD results in impaired conversion of 11-deoxycorticosterone (DOC) to corticosterone and 11-deoxycorticisol to cortisol. It leads to decreased synthesis of cortisol, which causes weakened depressant feedback of ACTH and increased synthesis of ACTH in the pituitary, leading to the overproduction and accumulation of more cortisol precursors (6). These steroid precursors are shunted into the adrenal androgen synthesis pathway, which leads to hyperandrogenism. Androgen excess results in precocious pseudopuberty, rapid somatic growth, a short adult stature and premature epiphyseal closure (7). The accumulation of DOC, which binds to and activates mineralocorticoid receptors, leads to hypertension and hypokalemia (6). There is a poor correlation between DOC secretion and the presence of hypertension. The degree of hypertension is variable (5).

The disease is divided on clinical grounds into classical and nonclassical forms. The accurate prevalence of the nonclassic form, a milder form, is unknown due to its rarity (2). Moreover, it is difficult to detect nonclassic 11β OHD because patients have either no symptoms or only mild symptoms. In the present case, on initial presentation, we suspected only a diagnosis of TPP caused by Graves’ disease because the patient was a young Asian man with hypokalemia, a low potassium excretion rate, a normal acid base balance and increased levels of thyroid hormones (8). However, our patient had prominent diastolic hypertension and hypokalemia as compared to that observed in general TPP patients. We conducted further examinations and found previously unrecognized nonclassic 11β OHD.

Thyroid hormones increase the turnover of cortisol (3). Administration of chronic high doses of T3 in rats increases the plasma and adrenal corticosterone levels (9). In our case, the increased thyroid hormone levels caused by Graves’ disease could have increased the turnover of cortisol, which may have triggered the adrenocortical steroidogenesis. When adrenocortical steroidogenesis is stimulated under nonclassic 11β OHD, the production of steroid precursors such 11-DOC can be anticipated to increase. Therefore, in the present case, the symptoms of occult nonclassic 11β OHD, including hypertension and hypokalemia, seem to have aggravated the symptoms of TPP. Takasu et al. reported a case of Graves’ disease caused an adrenal crisis in a patient with previously unrecognized nonclassic 21 hydroxylase deficiency (10). Increased levels of thyroid hormone may play an etiologic role in the development and aggravation of symptoms if unrecognized nonclassic congenital adrenal hyperplasia is present.

Nonclassic 11β OHD is caused by the partially impaired function of CYP11B1 (2). We detected two hypofunctional genetic polymorphisms of the CYP11B1 gene, including c.128 G>A and c.595+12 G>A. The c.128 G>A polymorphism has been previously described and it has been shown to result in a residual CYP11B1 activity level of approximately 30-50% (11). It is unclear if these genetic polymorphisms may be associated with mild or late onset symptoms. There is a poor correlation between the genotype and phenotype of nonclassic 11β OHD (12). The vast majority of mutations are associated with classic 11β OHD, and only a few mutations that cause nonclassic 11β OHD have been described (2, 13, 14).

The treatment of 11β OHD involves glucocorticoid administration to replace a deficient cortisol level and normalize ACTH, which in turn removes the drivers for oversecretion of DOC (15). In adults with nonclassic 11β OHD, treatment needs to be selected by considering the patient’s symptoms and balancing the potential benefits of treatment with the risks of iatrogenic Cushing’s syndrome. Asymptomatic adults with nonclassic 11β OHD do not universally require glucocorticoid treatment (16). Although the lack of adrenal steroid precursors values at euthyroidism is a limitation in our report, our patient had no symptoms, including hypertension, after normalization of his thyroid function.

The present case demonstrates the process of thyrotoxic periodic paralysis with Graves’ disease leading to the discovery of hidden nonclassic 11β OHD. Nonclassic 11β OHD is often an elusive diagnosis. Physicians should suspect that another precipitating disease such nonclassic 11β OHD could therefore be present when a TPP patient exhibits prominent hypertension or hypokalemia. The possibility of the coexistence of two such conditions should therefore be considered.

The authors state that they have no Conflict of Interest (COI).

References


