Case Report

Congenital Hypopituitarism due to POU1F1 Gene Mutation

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POU1F1 (Pit-1; Gene ID 5449) is an anterior pituitary transcriptional factor, and POU1F1 mutation is known to cause anterior pituitary hypoplasia, growth hormone and prolactin deficiency, and various degree of hypothyroidism. We report here a patient who presented with growth failure and central hypothyroidism since early infancy. However, treatment with thyroxine gave no effect and he subsequently developed calf muscle pseudohypertrophy (Kocher-Debre-Semelaigne syndrome), elevation of creatinine kinase, dilated cardiomyopathy, and pericardial effusion. Final diagnosis was made by combined pituitary function test and sequencing analysis that revealed POU1F1 gene c.698T>C (p.F233S) mutation. The rarity of the disease can result in delayed diagnosis and treatment.

Key Words: growth hormone deficiency, hypopituitarism; hypothyroidism, POU1F1

Development of the pituitary gland requires a cascade of signaling molecules and transcription factors. To date, nine major genes that are involved in hypothalamo-pituitary development have been recognized, including HESX1, SOX2, SOX3, GLI2, LHX3, LHX4, TBX19, PROP1, and POU1F1. Among these, mutations of PROP1 cause panhypopituitarism; POU1F1 mutation causes growth hormone (GH), prolactin, and thyroid stimulating hormone (TSH) deficiencies, whereas mutations of other genes cause specific syndromes, for example, mutation on HESX1 results in septooptic dysplasia.1,2

The POU1F1 gene (Pit-1; Gene ID 5449) is a tissue-specific transcriptional factor and belongs to the POU homeodomain family. It regulates GH, prolactin and TSH β-subunit gene expression, and somatotroph, lactotroph, and thyrotroph development of the anterior pituitary gland.1,3 Mutations of POU1F1 account for 7.8% of combined pituitary hormone deficiency (CPHD) and isolated GH deficiency.4 Clinical manifestations

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of **POU1F1** gene mutation include early growth failure, short stature, various degrees of mental retardation, characteristic facial features (prominent forehead, marked mid-face hypoplasia, saddle nose, deep-set eyes, short nose, and anteverted nostrils), and failure to thrive in infancy. The age of onset in TSH deficiency is variable, whereas prolactin deficiency does not manifest clinically in childhood. Hypoplastic pituitary gland can be found by brain magnetic resonance imaging (MRI), which confirms the role of this transcriptional factor in pituitary development. These patients respond to GH and thyroid hormone replacement. Since the first report in 1992, about 28 **POU1F1** mutations, mostly missense/nonsense mutations, have been reported in over 60 patients.

In this article, we report one case of **POU1F1** gene mutation that was misdiagnosed as isolated central hypothyroidism. Treatment with thyroxine was interrupted due to lack of efficacy, and the patient developed frank hypothyroidism including the Kocher-Debre-Semelaigne syndrome, a very rare disease, but a correct diagnosis is required before effective treatment can be instituted.

**Case Report**

A girl aged 2 years and 2 months, G4P3AA3, was born after 37 weeks of an uncomplicated pregnancy. Both parents were aboriginal Taiwanese, and their height and mentality were normal. Her birth weight was 3170 g (75th–90th percentile), birth length 48 cm (50th percentile), and birth head circumference 34 cm (75th–90th percentile). Apgar score was 7 at 1 minute and 9 at 5 minutes. Newborn screening for congenital hypothyroidism was normal.

Feeding difficulty was noted shortly after birth, and a heart murmur was found accidentally at the age of 4 months. At referral, she had severe failure to thrive (weight 3320 g; <3rd percentile; height 47.5 cm, <3rd percentile), developmental delay, poor oral intake, and hypotonia. Further evaluations revealed normocytic anemia (hemoglobin 6.7 g/dL, mean corpuscular volume 98.9 fL), and elevations of alanine aminotransferase (54 U/L, normal: <41 U/L), aspartate aminotransferase (91 U/L, normal: <37 U/L), creatinine kinase (440–1346 U/L, normal: <193 U/L), and lactate dehydrogenase (259–868 U/L, normal: 230–460 U/L). She had hypothermia, but normal pulse and respiration. Cardiac echo did not show any specific findings. Renal echo showed bilateral small kidneys. The 24-hour urinalysis showed decreased creatinine clearance (26 mL/min/1.73 m², normal: 40–65 mL/min/1.73 m²). Free thyroxine was <0.24 ng/dL (normal: 0.6–1.75 ng/dL), thyroxine was 0.13 μg/dL (normal: 6.1–14.9 μg/dL), triiodothyronine was 1.99 ng/dL (normal: 75–260 ng/dL), and TSH was 0.021 μIU/mL (normal: 0.1–0.45 μIU/mL). Brain MRI showed normal sella turcica, intact pituitary stalk, and sunken diaphragma sella (Figure 1, arrow). Sick euthyroid syndrome was the initial diagnosis. However, because of her poor growth, 25 μg/day thyroxine (7.5 μg/kg/day) was prescribed. Her growth did not improve, and the medication was stopped at the age of 1 year 6 months. Karyotype analysis showed normal female pattern (46,XX).

When we saw her again at the age of 2 years and 2 months, she had severe, proportional failure to thrive (weight 5.9 kg, height 59 cm, and head circumference 41.6 cm, all far below the 3rd percentile), wide anterior fontanelle (4.5 × 4.5 cm), and pale conjunctiva. In addition, she had fine and coarse hairs, small mouth, low set ears, and broad nasal bridge. Cardiac echo showed normal cardiac function. Cardiac catheterization showed normal coronary arteries. Brain MRI showed normal brain and pituitary gland. **POU1F1** gene mutation was identified by sequencing analysis. She was treated with thyroxine and growth hormone replacement.}

**Figure 1.** T1-weighted image of brain magnetic resonance imaging. Sagittal view showed normal sella turcica, intact pituitary stalk, and sunken diaphragma sella (arrow).
sparse hair, prominent forehead, deep-seated eyes, saddle nose with anteverted nostrils, poor tooth growth, bilateral calf muscle pseudohypertrophy, and mottling skin (Figure 2). She was alert but could only make repetitive consonant sounds. She stood with support and used a spoon for meals. She grew 11.5 cm in 22 months (growth rate: 6.2 cm/year). Chest X ray showed cardiomegaly, and echocardiography demonstrated left atrial and ventricular dilation, and pericardial effusion. Her bone age was only 6 months at a chronological age of 2 years 2 months. Brain MRI and blood biochemistry revealed similar findings as the previous studies at 4 months old, except that her creatine kinase levels was higher (970–2954 U/L). Her calf muscle hypertrophy was prominent. Free thyroxine (<0.24 ng/dL), TSH (<0.04 μIU/mL), and GH (<0.05 ng/mL) levels were all below the detection limits. A combined anterior pituitary function test was performed. Luteinizing hormone releasing hormone (100 μg), 100 μg thyrotropin releasing hormone, and 1 U insulin were given intravenously, and blood was drawn once every 30 minutes for 2 hours. The results showed normal cortisol and gonadotropin responses; however, the responses for GH, TSH, and prolactin were poor (Table). Therefore, hypopituitarism was diagnosed. Mutation analysis of POU1F1 revealed a homozygous c.698T>C (p.F233S) change (Figure 3).

**Figure 2.** Facial characteristics of the patient, showing fine and sparse hair, prominent forehead, deep-seated eyes, saddle nose with anteverted nostrils, and poor tooth growth.

**Figure 3.** Mutation analysis of POU1F1 revealed a homozygous c.698T>C (p.F233S) change in the patient and heterozygous on parents (arrows).

**Table.** Combined anterior pituitary function test by using 100 μg luteinizing hormone releasing hormone, 100 μg thyrotropin releasing hormone, and 1 U insulin

<table>
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<tr>
<th>Time (min)</th>
<th>Glu (mg/dL)</th>
<th>GH (ng/mL)</th>
<th>Cortisol (μg/dL)</th>
<th>TSH (μIU/mL)</th>
<th>Prolactin (ng/mL)</th>
<th>FSH (mIU/mL)</th>
<th>LH (mIU/mL)</th>
<th>Estradiol (g/mL)</th>
<th>Free T4 (ng/dL)</th>
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<td>&lt;0.15</td>
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Glu = glucose; GH = growth hormone; TSH = thyroid stimulating hormone; FSH = follicle stimulating hormone; LH = luteinizing hormone; T4 = thyroxine.
POU1F1 gene mutation and hypopituitarism

Discussion

In this report, we describe a case of POU1F1-mutation-induced CPHD with an initial presentation of retarded growth. Ineffective treatment due to severe TSH deficiency and poor compliance to medication led to a full-blown manifestation of hypothyroidism, including skeletal myopathy, and cardiomyopathy. Retrospectively, the characteristic facial dysmorphism might have been a clue for the early diagnosis of this rare disorder. A high index of suspicion is mandatory for early diagnosis, as well as replacement therapy with thyroid hormone and GH to prevent serious complications in these patients.

POU1F1 has three functional domains: a transactivation domain, a POU-specific, and a POU-homeo domain. The latter two domains are DNA-binding homeodomains.3,6,11 POU1F1 mutations and inheritance are heterogeneous. Mutations in the DNA-binding domains result in inactivation of POU1F1 protein and autosomal recessive inheritance. On the other hand, mutations in other regions, inherited as autosomal dominant, can lead to competitive inhibition of the mutant/wild-type heterodimer.1,4,12 In general, recessive mutations are more severe than their dominant counterparts. Currently, more than 28 POU1F1 mutations have been found in > 60 patients.2 As far as we are aware, the c.698T>C (p.F233S) mutation has not been reported before. Mutation of F233L has been reported in a twin with CPHD.13 F233 is located at the homeodomain of POU1F1 and is a DNA-binding site for transcription factors that control development and differentiation.11,13 The location of the amino acid (F233) is highly conserved and substitution of this amino acid can result in defects in correct folding, DNA binding, or other protein interactions.13

Certainly, there is more to be learned of this disease, such as the etiology of its neurological manifestations. Careful observation and management of more cases will help us to understand development of the pituitary gland and the brain.

References