Aniridia with a Heterozygous PAX6 Mutation in which the Pituitary Function was Partially Impaired

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Abstract

We herein report the case of a woman with aniridia and with a heterozygous PAX6 mutation. Pax6 is a transcription factor involved in the development of several organs, including the eye, pancreas and pituitary. The patient had been diagnosed with aniridia in childhood and was found to have impaired glucose tolerance with a heterozygous PAX6 mutation 12 years prior to the current admission. Hormone stimulating tests revealed a slightly impaired pituitary function, including subtle hypogonadotropichypogonadism and borderline growth hormone (GH) deficiency. The present case is the first report of a slightly impaired pituitary function in an aniridia patient with a heterozygous PAX6 mutation.

Key words: pituitary, PAX6, mutation

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Introduction

Pax6 is a highly evolutionally conserved transcription factor involved in the development of the eye, central nervous system and pancreatic islets (1-3). Mice with a targeted disruption of Pax6 die soon after birth, lacking eyes and exhibiting a marked reduction in the number of pancreatic islet cells (4, 5). In addition, it has been reported that Pax6 is involved in the development of the pituitary, and its homozygous mutation causes hypopituitarism in rodents (6, 7). On the other hand, in humans, a heterozygous mutation of PAX6 causes aniridia and impaired glucose tolerance or diabetes (8-10). However, there have been few reports evaluating the pituitary function in aniridia patients with heterozygous PAX6 mutations. We herein present the case of an aniridia patient with a heterozygous PAX6 mutation whose pituitary function was partially impaired.

Case Report

A 40-year-old woman with aniridia was referred to our department for an examination of her pituitary function. In childhood, she was diagnosed with aniridia and had been followed at an eye clinic at our hospital since then. She grew in stature normally and experienced menarche at 12 years of age. At 28 years of age, she was noted to have impaired glucose tolerance on a 75-g oral glucose tolerance test (75gOGTT). At that time, we screened her for the PAX6 gene mutation using direct DNA sequencing after obtaining her written consent, the results of which revealed a heterozygous mutation (c.969C>T) (9). The c969C>T mutation in the patient was a C>T substitution at codon 203 of exon 8 of the PAX6 gene that converts an Arg codon (CGA) to a termination codon (TGA), thereby leading to a truncated protein lacking a transactivation domain. As a result, the mutant did not exert any transcriptional activity (9).

On admission, the patient measured 165 cm in height and 86 kg in weight and was asymptomatic. Her blood pressure

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Table 1. Laboratory Data on Admission

<table>
<thead>
<tr>
<th>WBC  3.190 /μL</th>
<th>BUN 15.0 mg/dL</th>
<th>LH 1.9 mIU/mL (normal range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC  4.19 × 10^12 /μL</td>
<td>Cr 0.66 mg/dL</td>
<td>FSH 6.8 mIU/mL (1.5-10.8)</td>
</tr>
<tr>
<td>Hb  10.5 g/dL</td>
<td>UA 4.1 mg/dL</td>
<td>Estriadiol 3.0 ng/mL (14-251)</td>
</tr>
<tr>
<td>Ht  34.3 %</td>
<td>Na 138 mM/L</td>
<td>GH 0.14 ng/mL (0-2.7)</td>
</tr>
<tr>
<td>Plt  29.2×10^4 /μL</td>
<td>K 3.9 mM/L</td>
<td>IGF-1 122 ng/mL (98-245)</td>
</tr>
<tr>
<td>T-Bil 0.5 mg/dL</td>
<td>Ca 8.5 mg/dL</td>
<td>TSH 1.14 μU/mL (0.4-3.8)</td>
</tr>
<tr>
<td>AST 20 U/L</td>
<td>P 3 mg/dL</td>
<td>Free T3 2.4 pg/mL (2.0-3.4)</td>
</tr>
<tr>
<td>ALT 29 U/L</td>
<td>TG 105 mg/dL</td>
<td>Free T4 1.0 ng/dL (0.9-1.6)</td>
</tr>
<tr>
<td>ALP 154 U/L</td>
<td>HDL-C 47 mg/dL</td>
<td>Cortisol 2.7 μg/dL (4.2-20)</td>
</tr>
<tr>
<td>γ-GTP 27 U/L</td>
<td>LDL-C 115 mg/dL</td>
<td>DHEA-S 194.6 μg/dL (41.3-218.2)</td>
</tr>
<tr>
<td>CPK 82 U/L</td>
<td>Glucose 102 mg/dL</td>
<td>U-cortisol 47.8 μg/day (10-100)</td>
</tr>
<tr>
<td>TP 6.1 g/dL</td>
<td>HbA1c 6.1 %</td>
<td>PRL 5.4 ng/mL (4.6-35.0)</td>
</tr>
<tr>
<td>Alb 3.8 g/dL</td>
<td>CRP 0.07 mg/dL</td>
<td></td>
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</tbody>
</table>

Table 2. 75-g OGTT

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>PG (mg/dL)</th>
<th>IRI (μU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>111</td>
<td>10.3</td>
</tr>
<tr>
<td>30</td>
<td>177</td>
<td>38.9</td>
</tr>
<tr>
<td>60</td>
<td>207</td>
<td>58.2</td>
</tr>
<tr>
<td>90</td>
<td>194</td>
<td>63.8</td>
</tr>
<tr>
<td>120</td>
<td>184</td>
<td>59.5</td>
</tr>
</tbody>
</table>

PG: plasma glucose, IRI: immunoreactive insulin

was 108/70 mmHg, her heart rate was 68 beats/min and her body temperature was 36.8°C. She had a regular menstrual period and a history of three deliveries. Of her three children, one had aniridia. On the other hand, it was not clear whether her parents had aniridia. She had no past history accounting for acquired hypopituitarism, such as a brain injury, pituitary tumor, cranial irradiation, hypophysitis or glucocorticoid treatment. A physical examination demonstrated no significant findings, including loss of axillary and pubic hair, except for the lack of the bilateral irises. Chest radiography and electrocardiography were normal. The results of routine laboratory and urine tests were within the normal ranges, except for slight anemia (Table 1). A 75gOGTT revealed impaired glucose tolerance (Table 2). Magnetic resonance imaging (MRI) of the hypothalamus and pituitary gland disclosed no abnormal findings. As shown in Table 1, an endocrine examination performed in the morning (8:00 AM) after a 30-minute rest in the supine position showed that the serum cortisol level was slightly low (2.7 μg/dL) with a normal serum adrenocorticotropic (ACTH) level (13 pg/mL). On the other hand, the levels of urinary free cortisol, dehydroepiandrosterone-sulfate (DHEA-S) and other pituitary hormones were within normal ranges. On hormone stimulating tests, including those of thyrotropin-releasing hormone (TRH, 0.5 mg), luteinizing hormone (LH) releasing hormone (LH-RH, 0.1 mg) and insulin (regular insulin 10 units [0.12 u/kg]), thyroid stimulating hormone (TSH), prolactin (PRL), ACTH and cortisol exhibited normal responses, whereas LH and follicle stimulating hormone (FSH) exhibited low responses and growth hormone (GH) exhibited a subnormal response (Figure A, B, C). Additionally, on the growth hormone-releasing peptide 2 (GHRP-2, 0.1 mg) stimulating test, GH exhibited a low response (Figure D). These findings suggest that the patient had subtle hypogonadotropic hypogonadism and borderline GH deficiency.

Discussion

In this report, we presented a case of aniridia with a heterozygous PAX6 mutation in which the patient’s pituitary function was slightly impaired. To our best knowledge, this is the first report to evaluate the pituitary function and find a slightly impaired pituitary function in an aniridia patient with a heterozygous PAX6 mutation.

Aniridia is a rare congenital eye anomaly characterized by a variable degree of iris hypoplasia that is often associated with cataracts, optic nerve hypoplasia and glaucoma. Approximately two-thirds of aniridia cases are familial with an autosomal dominant inheritance, while the remaining one-third are sporadic (11). In the familial cases, the penetrance is high, although the expressivity is variable. Genetically, PAX6 gene mutations are the only known cause of aniridia identified to date (12). The human PAX6 gene, spanning 22 kb of genomic DNA, contains 14 exons and encodes 422 amino acids. The gene has paired and homeobox DNA-binding domains followed by a proline-, serine- and threonine-rich transactivation domain at the C-terminus (13, 14). Pax6 is a highly evolutionally conserved transcription factor involved in the development of the eye, central nervous system and pancreatic islets (1-3). Mice with a targeted disruption of Pax6 die soon after birth, lacking eyes and exhibiting a marked reduction in all four types of endocrine cells (α, β, δ and pancreatic polypeptide cells) in the pancreas, thereby leading to markedly reduced hormone production (4, 5). In addition, recent studies have shown that Pax6 is crucial for β-cell functions by regulating transcription factors involved in insulin biosynthesis and secretion as well as the actions of glucose and incretin on β-cells (15-17). Furthermore, there have been several reports that aniridia patients with heterozygous PAX6 mutations have abnormal glucose tolerance or diabetes with a reduced insulin response on OGTT (9, 10). Therefore, the patient’s impaired glucose tolerance with a delayed insulin response to a 75gOGTT may have been due to the PAX6 mutation.
However, because the patient has obesity, and the association between the PAX6 mutation and abnormal glucose tolerance in the proband’s family was not clear, possible causes of the patient’s impaired glucose tolerance other than the PAX6 mutation cannot be completely excluded.

On the other hand, it has also been reported that Pax6 is expressed and involved in the development of the pituitary gland (6, 7). The pituitary gland is a midline structure located within the sella turcica recess of the sphenoid bone at the base of the brain. The development of the anterior pituitary gland is characterized by a highly complex and organized process involving temporary and spatially arranged signaling molecules and tissue-specific transcription factors, such as HESX1, LHX3, LHX4, PROP1, PIT1, GATA2 and TBX19 (18-20). The mature anterior pituitary gland consists of five distinct cell types, secreting a total of six hormones: LH and FSH from the gonadotrophs, GH from the somatotrophs, TSH from the thyrotrophs, ACTH from the corticotrophs and PRL from the lactotrophs. It has recently been shown that mutations of several transcription factors involved in the development of the pituitary gland result in impaired pituitary formation and hypopituitarism (18). For example, patients with HESX1 mutations exhibit isolated GH deficiency or combined pituitary hormone deficiency and variable MRI abnormalities ranging from a structurally normal pituitary to a more severe radiological phenotype characterized by anterior pituitary hypoplasia. On the other hand, Pax6 is also expressed in the pituitary gland and has been found to be involved in the development and function of the pituitary gland. An analysis of Pax6 homozygous mutant mice (Sey<sup>nu</sup>) revealed a marked decrease in the number of terminal differentiated dorsal somatotrope and lactotrope cells and the serum levels of GH and PRL (6, 7). This result not only suggests the important role of Pax6 in the development and function of the pituitary gland, but also raises the possibility that the PAX6 mutation results in hypopituitarism. In humans, two patients with a compound heterozygous PAX6 mutation have been previously reported (3, 21). The first case, reported by Glaser et al., involved a female infant with compound heterozygous nonsense mutations in PAX6. The patient, who died at eight days of age, had severe craniofacial defects and no eyes. Her weight (1,900 g), height (44 cm) and head circumference (28.5 cm) were below the third centile. A postmortem examination revealed severe central nervous system defects. However, although the authors reported that the hypothala-

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**Figure.** Pituitary endocrine function tests. (A) A TRH loading test showed normal responses of TSH (○) and PRL (●). (B) An LH-RH loading test showed low responses of LH (○) and FSH (●). (C) An insulin tolerance test showed that the plasma glucose level decreased to the minimum (26 mg/dL) after 30 minutes. ACTH (●) and cortisol (○) exhibited normal responses, whereas GH (□) exhibited a subnormal response (peak GH level: 3.29 ng/mL). (D) A GHRP-2 loading test showed normal responses of ACTH (●) and cortisol (○) with a low response of GH (□) (peak GH level: 7.99 ng/mL).
mus was truncated abnormally with an expanded infundibulum and pituitary stalk, the morphology of the pituitary gland and the serum levels of pituitary hormones were not described (3). Therefore, it is unknown whether the patient had an impaired pituitary function. The second case, reported by Solomon et al., involved a 4-year-old boy who was a member of a large bilinear family with eye anomalies. The patient had inherited a different mutation in PAX6 from each parent. He had bilateral microphthalmia, choanal atresia and neonatal-onset insulin-dependent diabetes mellitus. In addition, he had hypopituitarism, including central hypothyroidism, hypogonadotropic hypogonadism and secondary adrenal insufficiency. Brain MRI showed hypoplasia of the pituitary gland and hypothalamus. However, in that report, the serum GH, IGF-1 and PRL levels were not described (21). In addition, although the detailed causes are unclear, the impaired pituitary hormones (TSH, gonadotropins and ACTH) in this patient were different from those (GH and PRL) noted in Pax6 homozygous mutant mice. On the other hand, there have been few reports in the English literature evaluating the pituitary function in patients with a heterozygous PAX6 mutation. In the present case, although the basal pituitary hormone levels were within the normal ranges, hormone stimulating tests revealed slightly impaired responses of gonadotropins and GH. In addition, the patient had no past history accounting for acquired hypopituitarism, such as a brain injury, pituitary tumor, cranial irradiation, hypophysitis or glucocorticoid treatment. These findings and the above-mentioned role of Pax6 in the development and function of the pituitary gland suggest that the patient had subtle hypogonadotropic hypogonadism and borderzone GH deficiency possibly due to a heterozygous PAX6 mutation. However, this study is a single clinical case report, and the association between the PAX6 mutation and the pituitary function in the proband’s family was not evaluated. In addition, unknown causes of hypopituitarism other than the PAX6 mutation in the present case cannot be completely ruled out. Furthermore, the partial hypopituitarism in the patient was subtle, and she had no clinical symptoms. Therefore, it is not possible to conclude that a direct association exists between a heterozygous PAX6 mutation and hypopituitarism in humans based on this study. Taken together, further family and functional studies are needed to clarify the association between a heterozygous PAX6 mutation and impairment of the pituitary function.

In conclusion, we herein reported a case of aniridia with subtle partial hypopituitarism and a heterozygous PAX6 mutation. The present study is a pilot case report that evaluated the pituitary function in an aniridia patient with a heterozygous PAX6 mutation.

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

References