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Case Report

Hearing loss with two pathogenic *SLC26A4* variants and positive thyroid autoantibody: A case report

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Highlights

- This patient had two pathogenic *SLC26A4* variants and positive thyroid autoantibody.
- Pendred syndrome and Hashimoto's thyroiditis can coexist.

Abstract. *SLC26A4* causes Pendred syndrome (PS) and nonsyndromic hearing loss. PS is distinguished based on perchlorate discharge test abnormality, goiter, and hypothyroidism in some patients. The pathophysiology of thyroid dysfunction in PS differs from that of autoimmune thyroid disease, in that it is considered to be caused by an iodide organification defect. It is believed that both diseases may incidentally coexist, and that *SLC26A4* may play an important role in the etiology of autoimmune thyroid disease. Herein, we describe a case of a girl with hearing loss who had two pathogenic *SLC26A4* variants and tested positive for thyroid peroxidase (TPO) antibody. She was diagnosed with hearing loss and vestibular aqueduct enlargement at the age of 4 yr. Deafness gene screening revealed two pathogenic *SLC26A4* variants. As *SLC26A4* variants can cause PS, the patient underwent thorough thyroid examination. Her thyroid gland was within the physiological range of mild enlargement. Although thyroid function test results were normal, the patient tested positive for TPO antibody. The patient was diagnosed with "suspected PS" and "suspected Hashimoto's thyroiditis," both of which increase the risk of developing hypothyroidism. Evaluating the comorbidity of Hashimoto's thyroiditis with the *SLC26A4* variant in terms of complications is critical.

Key words: Hashimoto's thyroiditis, Pendred syndrome, *SLC26A4*, thyroid autoantibody

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Introduction

Congenital hearing loss is a relatively common disorder, that affects more than one child in every 1,000 births (1). Furthermore, the incidence of congenital hearing loss in children, including those who progress to progressive hearing loss during childhood, is estimated to be 2.7 per 1,000 children at 4 yr of age (2).

The pendrin protein, SLC26A4, is expressed in several tissues, including the thyroid, inner ear, and kidneys. Pendrin regulates pH in the inner ear and secretes bicarbonate in the kidneys (3, 4). In the thyroid, the sodium ion / iodine ion symporter mediates active iodine ion transport to follicular cells. Pendrin has since been linked to iodine ion transport into the follicular lumen (5, 6). Furthermore, thyroid peroxidase (TPO) oxidizes iodide ions, forming iodine atoms that are then added to tyrosine residues on thyroglobulin to produce thyroid hormones (7). *SLC26A4* is the gene that causes Pendred syndrome (PS) and nonsyndromic hearing loss (DFNB4: autosomal recessive nonsyndromic congenital deafness, locus 4). Both diseases are characterized by sensorineural hearing loss and vestibular aqueduct enlargement. In such cases, hearing loss occurs congenitally or during childhood, and immediate intervention is required because hearing loss can progress to bilateral hearing loss and become severe (4). Patients with PS develop goiters after the age of 10 yr, as well as abnormal perchlorate discharge test (PDT) results and hypothyroidism in some cases. The prevalence of PS is estimated to be 7.5 per 100,000 people. PS accounts for approximately 4%–10% of all cases of hereditary deafness and may be the most common cause of syndromic deafness (4).

Thyroid autoantibodies are found in patients with autoimmune diseases such as Hashimoto's thyroiditis (HT) and Graves' disease (GD) (8). The presence of thyroid autoantibodies against HT in the absence of thyroid dysfunction or goiter formation raises suspicion of HT. The pathophysiology of thyroid diseases caused by the pathogenic *SLC26A4* variant is distinct from that of autoimmune thyroid diseases (AITD). We herein present a case of a girl who had two pathogenic *SLC26A4* mutations and was positive for thyroid autoantibody.

Case Presentation

The patient was observed to have a delay in language acquisition during a health checkup at the age of 3 yr and 6 mo. She had no previous hearing or thyroid function abnormalities, or other underlying medical conditions. She had no family history of hearing loss or thyroid disease. Although the audiologist's examination revealed no hearing loss, her family noticed the girl's poor hearing at the age of 4 yr. Therefore, the patient was examined by an otolaryngologist and was diagnosed with hearing loss. She was referred to our hospital, where she was diagnosed with right-sided deafness and moderate left-sided hearing loss. Brain computed tomography performed at the age of 4 yr showed bilateral vestibular aqueduct enlargement (**Fig. 1**). She underwent right cochlear implantation at the age of 5 yr. The patient continued her auditory rehabilitation. She also had left-sided hearing deterioration at the age of 7 yr. Genetic analysis of 154 pathogenic variants in 19 hearing loss genes (*KCNQ4*, *OTOF*, *WFS1*, *SLC26A4*, *EYA1*, *CDH23*, *MYO7A*, *TECTA*, *GJB2*, *COCH*, *CRYM*, *MYO15A*, *ACTG1*, *TMPRSS3*, *POU3F4*, *MT-RNR1*, *MT-TL1*, *MT-TS1*, and *MT-TK*) was performed using next-generation sequencing and invader assay by BML Inc. (Tokyo, Japan). At 11 yr of age, a screening test for hearing loss genes identified two pathogenic variants in the *SLC26A4*; NM_000441.1:c.439A>G(;)2168A>G and NP_000432.1:p. Met147Val(;)His723Arg. These missense variants cause abnormal transcriptional functions and prevent anion exchange activity (9).

Her parents have not undergone any genetic tests. As the *SLC26A4* variant can cause PS, which can result in goiter and hypothyroidism, the patient underwent a thorough thyroid examination. On physical examination, her thyroid gland could not be seen but was palpated;

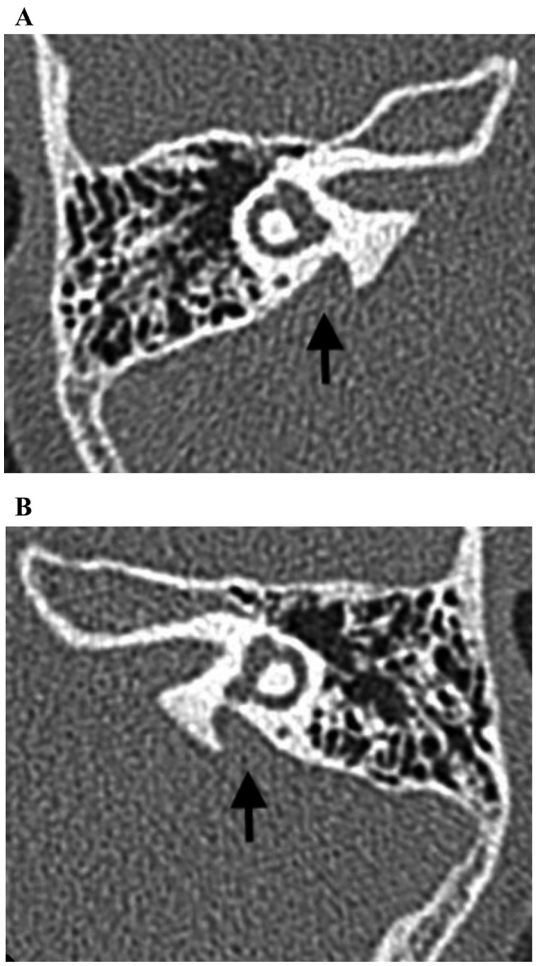

Fig. 1. Brain computed tomography reveals bilateral vestibular aqueduct enlargement. The diameter of the right vestibular aqueduct opening is 4.3 mm (A), while the left vestibular aqueduct opening is 4.0 mm (B) (arrow).

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thus, the Shichijo classification was first degree. No other physical abnormalities were observed. The WTAR (width multiplied by thickness of the area), width, and thickness of the thyroid gland measured by ultrasonography were expressed as standard deviation scores by body surface area (1.6 m^2) (10); the scores were 1.32, –0.40, and 2.50 for the right lobe and 0.84, –0.41, and 1.52 for the left lobe, respectively. The thyroid in our patient was slightly enlarged, but within the physiological range (**Fig. 2**). Laboratory analysis revealed that TSH and fT4 levels were within the normal range, and fT3 level were slightly higher than the reference range. She tested positive for anti-TPO antibodies (**Table 1**). Brain magnetic resonance imaging at 5 yr of age revealed bilateral vestibular aqueduct enlargement; however, no other inner ear malformations were observed (**Fig. 3**). The patient was suspected of having PS owing to bilateral hearing loss, vestibular aqueduct enlargement, and pathogenic *SLC26A4* variants. The patient was suspected to have HT because of positive TPO antibodies and a normal thyroid size. As we were concerned that either disease could lead to hypothyroidism, we decided to routinely follow-up the patient. At 16 yr of age, neither goiter nor hypothyroidism had developed.

Written informed consent for the genetic analysis and publication was obtained from the patient's parents. This study was authorized by the Ethics Committee of Tohoku University Hospital.

Discussion

We discovered two pathological variants in *SLC26A4*, the gene that causes PS, and positive thyroid

Table 1. Laboratory findings of the patient at the age of 11 yr

Biochemical analysis		
fT_4 (ng/dL)	0.97	0.90–1.70
fT_3 (pg/mL)	4.01	2.30–4.00
fT_3/ fT_4	4.13	
hTSH (μU/mL)	1.68	0.50–5.00
anti-Tg Ab (U/mL)	12.5	< 28.0
anti-TPO Ab (U/mL)	24.6	< 16.0

hTSH, human thyroid stimulating hormone; anti-Tg Ab, anti-thyroglobulin antibodies; anti-TPO Ab, anti-thyroid peroxidase antibodies.

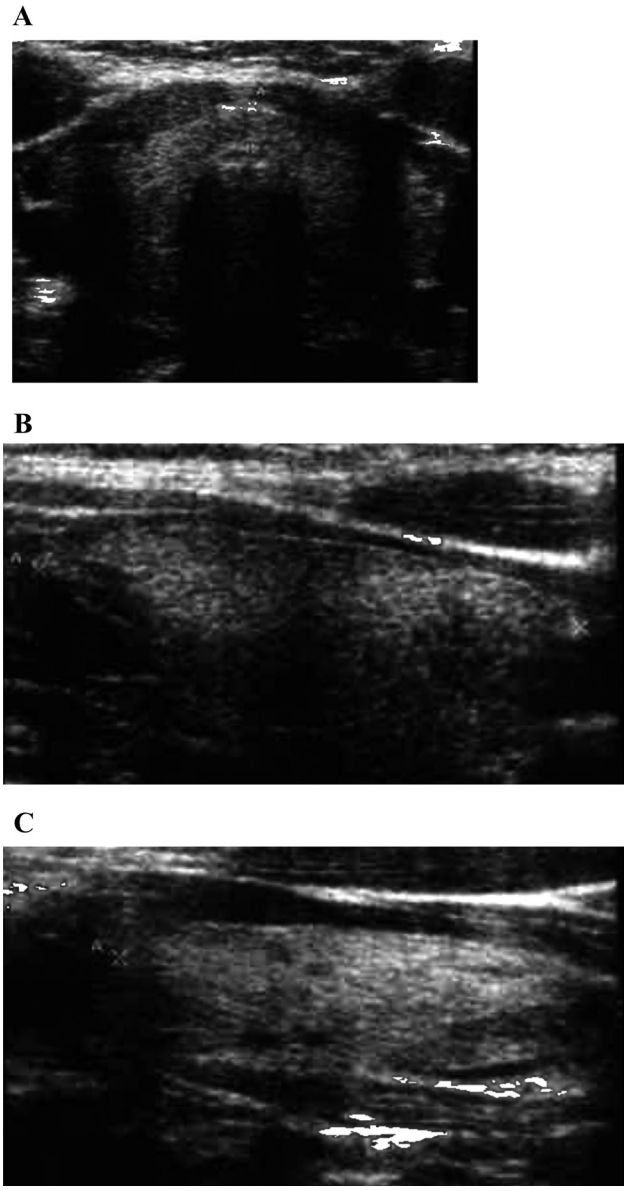

Fig. 2. Ultrasonographic images of the patient's thyroid glands. (A) Short axis view, (B) Right long axis view, (C) Left long axis view. Right lobe, 14.3 × 18.3 × 48.6 mm; Left Lobe, 14.2 × 14.2 × 45.4 mm; isthmus, 4.3 mm.

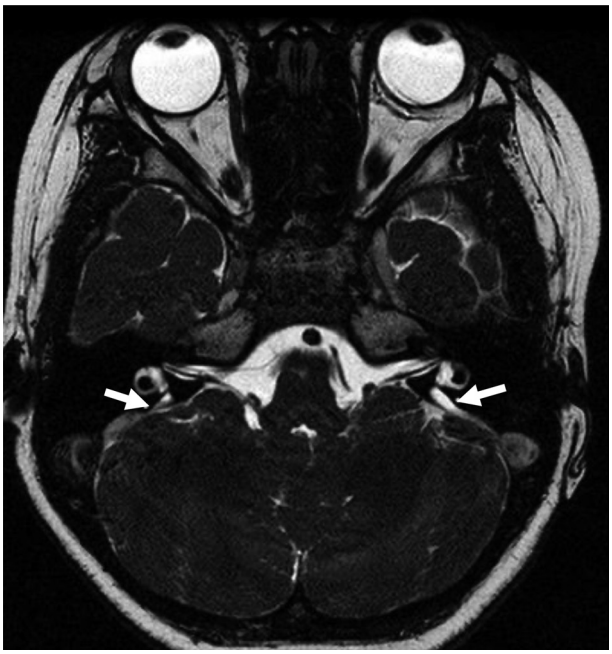

Fig. 3. Brain magnetic resonance imaging revealing bilateral vestibular aqueduct enlargement (arrows), but no other inner ear malformations.

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autoantibodies in a girl with hearing loss. This patient was diagnosed with DFNB4 and "suspected HT" because there was no obvious goiter. As there have been few reports of PS or DFNB4 complications in HT (11), we sought to demonstrate the associations between them by collecting sufficient data through genetic tests.

The presence of clinical signs of thyroid disease in PS distinguishes this phenotype from DFNB4. However, patients with DFNB4 may develop goiters over time and eventually be diagnosed with PS or patients with PS may have negative PDT results (12). Therefore, it is difficult to distinguish PS from HT in thyroid conditions. When a goiter is visible, the effects of both conditions must be carefully considered. Laboratory analysis in this case revealed that the TSH and fT4 levels were within the normal range, but the fT3 levels were slightly elevated. Therefore, the fT3/fT4 ratio was higher than that reported for healthy children (3.07 ± 0.38) (13). The conversion of fT4 to fT3 is reportedly enhanced by the increased activity of iodothyronine deiodinase 1 and 2 in PS and HT with thyroid gland enlargement (14, 15), therefore it is possible that the fT3/fT4 ratio was increased by the same mechanism in this case.

The screening test for hearing loss that this patient underwent has been covered by insurance since 2015, and now allows the analysis of 1,135 pathogenic variants in 50 hearing loss genes that are characteristic and common among Japanese patients with hearing loss. *SLC26A4* is the second most frequently detected gene, trailing only gap junction protein beta 2 (*GJB2*) gene, among Japanese patients with hearing loss (16). A total of 487 pathogenic *SLC26A4* variants have been identified (Deafness Variation Database: https://deafnessvariationdatabase.org/gene/*SLC26A4*/) (17). Furthermore, p. His723Arg is the most common mutation among Japanese patients (12).

In this case, possible explanations for the absence of goiter include iodine intake and the involvement of compensatory mechanisms by anoctamin 1 (ANO1). The pathophysiology of goiter in PS has been identified as a partial iodide organification defect (18). However, it is unclear why these phenotypes vary widely among the studies. A previous study found no correlation between the genotype and phenotype (12). Conversely, dietary iodine deficiency is linked to an increased risk of goiter in patients with PS (4). Indeed, Asian regions with high iodine consumption reportedly have a lower incidence of PS-related goiter than European regions (12, 19, 20). Furthermore, ANO1 has been linked to the same role as that of pendrin and may be part of a redundant system. ANO1 is a calcium-activated chloride channel that is present in many tissues, and facilitates iodide release (4). This compensatory mechanism may explain why goiters remain asymptomatic until the second decade of life. There may be differences in the age of onset and frequency, depending on the compensation period. The absence of goiter in our case could be attributed to redundant ANO1 system and iodine intake.

SLC26A4 and AITD may have a mutual influence. Although pendrin and TPO are expressed on the apical membranes of thyroid cells facing the follicular lumen, their functions are distinct. Therefore, the pathophysiological mechanisms of PS and TPO antibody-positive HT differ. Conversely, the genetic implications of *SLC26A4* in the susceptibility to AITD have been previously reported (21). In a study of *SLC26A4* transcript levels in thyroid tissues from patients with various thyroid pathologies, expression levels were increased in GD (mean: 27.17-fold higher than normal thyroid tissues) and decreased in HT (means: 92.05-fold lower than normal thyroid tissues) (22). Furthermore, a Tunisian study that examined the variation spectrum of *SLC26A4* in the thyroid tissue of patients with AITD found that 47% and 37.5% of patients in the GD and HT groups, respectively, carried at least one heterozygous variation. None of these variants is considered pathogenic; however, they include nonsynonymous variants that have already been reported in patients with symptomatic or isolated hearing loss in a heterozygous state (23). This suggests that even genetic polymorphisms that are nonpathogenic may affect the development of AITD.

Differentiating PS from HT is critical for proper follow-up. If a patient with hearing loss is diagnosed with the *SLC26A4* variant, genetic counseling may be beneficial owing to its autosomal recessive inheritance. During this period, the possibility of goiter development as a PS should be discussed. However, even patients with hearing loss carrying the *SLC26A4* variant may develop goiter as a result of HT. Therefore, during goiter evaluation, antibody testing for AITD should be performed. If HT is diagnosed, further testing for autoimmune complications, such as type 1 diabetes mellitus and Sjögren's syndrome, is required. Conversely, because hearing loss is an inevitable symptom of PS, there is no compelling reason to consider PS in cases of goiter alone.

Conclusion

We present a case of a girl who had two pathogenic *SLC26A4* variants and was positive for thyroid autoantibodies. Notably, goiter may develop in some *SLC26A4* pathogenic variants. Screening for thyroid autoantibodies in patients with pathogenic *SLC26A4* variants is critical for accurate diagnosis and treatment of HT complications.

Conflict of interests: The authors have no competing interests to declare.

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