Case report

Pendred syndrome with hyperthyroidism

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Abstract

Objectives: Pendred syndrome is an autosomal recessive disorder characterized by the combination of sensorineural deafness and goiter and is caused by biallelic mutations in the SLC26A4/PDS gene. Thyroid function is generally reported as euthyroid or hypothyroid in this condition. We present a case of Pendred syndrome with hyperthyroidism.

Patient: An 83-year-old woman with congenital deaf-mutism presented with complaints of nausea. She developed a large goiter and had hearing impairment. Her hearing level was 105 dB in both ears. She presented with hyperthyroidism and was treated with thiamazole.

Results: She had a homozygous mutation in c.1579A>C:p.T527P of the SLC26A4 gene, confirming a diagnosis of Pendred syndrome.

Conclusion: Pendred syndrome may develop into hyperthyroidism if the size of the goiter increases. Moreover, a homozygous mutation in c.1579A>C:p.T527P of the SLC26A4 gene, which was previously reported to be associated with nonsyndromic hearing loss with enlarged vestibular aqueduct, may also cause Pendred syndrome.

Key words: Pendred syndrome, hyperthyroidism, SLC26A4 gene

Introduction

Pendred syndrome (PS) was first described by Vaughan Pendred in 1896. It is an autosomal recessive disorder characterized by congenital sensorineural hearing loss, goiter, and impaired iodide organification. PS is caused by homozygous or compound heterozygous mutations in the SLC26A4 gene, located on chromosome 7q. Mutations in the SLC26A4 gene are known to be responsible for a broad phenotype spectrum, from typical PS to nonsyndromic hearing loss with enlarged vestibular aqueduct (NSEVA). The difference between PS and NSEVA is the presence of goiter or thyroid dysfunction. Most patients with PS are euthyroid or hypothyroid. However, in the case presented here, we encountered a patient diagnosed with PS with hyperthyroidism.

Case Report

Informed consent for the publication of this report was obtained from the patient and her family. An 83-year-old woman with congenital deaf-mutism presented with complaints of nausea. Her hearing level was 105 dB in both ears. It was unclear if her parents had consanguineous marriage. Three of her eight siblings had hearing impairment, but their thyroid abnormalities were unknown.

At the age of 63 years, the patient was diagnosed with goiter, but her thyroid function was unknown. At the age of 76 years, she was admitted to our hospital because of frequent vomiting. Medical examination results indicated that she had a large goiter with irregular palpable nodules. Laboratory tests revealed the following results: free thyroxine level, 3.81 ng/dL (normal range, 0.70–1.48 ng/dL); free triiodothyronine level, 7.21 pg/mL (normal range, 1.71–3.71 pg/mL); thyroid-stimulating hormone (TSH) level, 0.01 μU/mL (normal range, 0.35–4.94 μU/mL); thyroglobulin antibody level, 12.0 U/mL (normal range, 0–27 U/mL); thyroid peroxidase antibody level, 8.0 IU/mL (normal range, 0–16 IU/mL); thyrotropin receptor antibody (TRAB) level, <1.0 IU/L (normal range, <2.0 IU/L); TSH-stimulating antibody level, 93% (normal range <120%); and thyroglobulin level, 460 ng/mL (normal range, 0.0–32.7 ng/mL). Computed tomography (CT) scan showed that her goiter was calcified.

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with numerous nodules. She was discharged from our hospital after her symptoms improved.

When the patient was 77 years old, her thyroid hormone state (THS) level was high; hence, she started taking a daily dose of 10 mg thiamazole. Three months later, her THS level decreased, and her thiamazole dose was reduced to only 5 mg/day. Since then, her THS level has fluctuated slightly, and her serum thyroglobulin level has gradually increased. However, her serum TRAB level was within the normal range (Figure 1). She was advised to have a thyroidectomy, but she refused to undergo the procedure because of old age.

At the age of 83 years, the patient was readmitted to our hospital due to frequent vomiting. Based on her medical examination and CT scan results, her goiter was further enlarged (Figures 2 and 3). Her ultrasound scan showed an enlarged thyroid gland with multiple nodules of varying echogenicities. The largest nodule, measuring $24 \times 24 \times 61$ mm, was located in the right lobe (Figure 4). Fine needle aspiration of this nodule demonstrated adenomatous goiter (Figure 5).

A thyroid scintiscan indicated that the patient’s thyroid uptake increased, mainly in the upper and middle regions of the right thyroid lobe, and that tracers were markedly heterogeneously distributed in the goiter (Figure 6). According to our calculation, the uptake rate was 25.5% (normal range, 0.5–4.0%). Based on the patient’s axial high-resolution temporal bone CT images, malformation of the inner ear with an enlarged vestibular aqueduct and a Mondini cochlea were not detected. In this study, magnetic resonance imaging of the auditory canals was not performed.

With the consent of the patient and her family, genetic testing was performed by BML Corporation using the ion

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**Figure 1** Clinical course and transition of thyroid function.

**Figure 2** The goiter of the patient.

**Figure 3** Neck computed tomography showing the largest nodule in the right thyroid lobe.

**Figure 4** Ultrasound scan showing the largest nodule in the right thyroid lobe.

PGM system developed by Life Technologies Corporation. A homozygous mutation in c.1579A>C:p.T527P of the SL-C26A4 gene was observed, confirming a diagnosis of PS.
Discussion

In this case study, we found two important clinical findings. First, PS can develop into hyperthyroidism if the size of the goiter increases. PS is caused by biallelic mutations in the SLC26A4/PDS gene encoding pendrin, which is a multifunctional anion exchanger\textsuperscript{\textsuperscript{10}}. In the thyroid, pendrin is expressed at the apical membrane of thyroid cells facing the follicular lumen and mediates the iodide efflux\textsuperscript{11, 12}. Abnormal pendrin causes different thyroid hormone synthesis disorders such as hypothyroidism\textsuperscript{4}. This disorder is most commonly observed in patients with PS, while approximately half of PS cases do not cause hypothyroidism\textsuperscript{9, 13}. This suggests that PS can cause different thyroid hormone synthesis disorders. For iodide transport, anoctamin 1 in the thyroid follicular cells may contribute to the delivery of iodide into the follicular lumen for the synthesis of thyroid hormones, independent of pendrin\textsuperscript{14}. In the present study, our patient experienced hyperthyroidism for a long time, leading to goiter formation. Based on the normal thyroid autoantibodies observed, Hashimoto’s disease or Graves’ disease was not observed in this patient. Therefore, some of her thyroid nodules were presumed to excessively produce thyroid hormones. However, the hormone-producing ability of these nodules was low because her thyroid hormone level was controlled with a small amount of thiamazole.

Second, a homozygous mutation in c.1579A>C:p.T527P of the SLC26A4 gene causes PS. SLC26A4 was identified as a PS-causing gene\textsuperscript{4, 5}, and various mutations (including missense, nonsense, splice site, and frameshift) in this gene have hitherto been described\textsuperscript{15–19}. The mutation allele, p.T527P, has been reported\textsuperscript{20}. However, in that case, the nucleotide change was c. 1579A>G, the SLC26A4 mutation was considered a compound heterozygous mutation for p.T527P/H723R, and the phenotype was NSEVA without any goiter\textsuperscript{7, 20}. Moreover, a similar mutation allele, p.T537P, has been reported, whereby SLC26A4 underwent compound heterozygous mutation for p.T537P/H723R and the phenotype was PS with large goiter but normal THS\textsuperscript{21}. This is the first study to identify that the homozygous mutation in c.1579A>C:p.T527P of the SLC26A4 gene causes PS.

In summary, we present an elderly patient diagnosed with PS with hyperthyroidism and a missense mutation in the SLC26A4 gene. Additionally, the clinical course of PS has never been observed in any elderly patient as in our study. In PS patients, goiters gradually increase in size and may cause hyperthyroidism if the goiters are sufficiently large. Therefore, thyroidectomy is required at an appropriate time.

Conflict of interest: The authors state that they have no conflict of interest.
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