

## CLINICAL VIGNETTE

# Bilateral Hearing Loss and Goiter in a Young Female with Hashimoto's Thyroiditis

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### Case Presentation

A 38-year-old female who has a history of bilateral sensorineural hearing loss since childhood presents to endocrine for management of post-surgical hypothyroidism, which developed after undergoing a right thyroidectomy for a “golf ball” sized nodule. Final surgical pathology was benign. Patient reports when she was 26-years-old she had a right thyroid nodule that was causing dysphagia. She had been noted even in her teenage years to have a full thyroid gland by her family members. At that point, she sought medical advice and was told she had Hashimoto's thyroiditis with positive antiTPO antibodies. She did not require thyroid replacement. She was found with a right-sided thyroid nodule. She had mentioned that the nodule was causing hoarseness and dysphagia. She had undergone an ultrasound-guided fine needle aspiration of the right thyroid nodule. Pathology results were indeterminate at the time; however, thyroid surgery was recommended, and she underwent a right thyroidectomy. She required thyroid replacement post-surgery and was started on levothyroxine the dose of which has increased over time. Currently, she is on levothyroxine 150mcg daily.

Meanwhile, the patient has been experiencing bilateral hearing loss since she was approximately 9-years-old. She was a full-term baby, and as a baby and toddler, she did not exhibit signs of hearing loss while meeting her developmental milestones. After the first-grade, she was noted to have trouble with her hearing and had frequent, what were thought to be at the time, ear infections. She denies having had vertigo, nausea, or vomiting, which can be associated with Meniere's disease (can present with bilateral hearing loss). At first she was told she had dysfunction of her Eustachian tube and that her hearing impairment was due to chronic sinusitis and frequent ear infections. However, over the years her hearing loss became worse, and at age 30, she required bilateral hearing aids. She had gone to multiple ear, nose, and throat surgeons over the years without a clear answer as to why she had hearing loss. It was not until she went to a nationally recognized hearing institute that she was evaluated for genetic causes of hearing loss two years ago, approximately 8-years after she started wearing hearing aids.

Testing began with a panel of labs for childhood sensorial hearing loss. On pure tone audiometry, she had bilateral moderate to severe high frequency sensorial neural hearing loss (SNHL). She was tested for Anti-68kD antibodies, which are positive in 35% of patients with progressive SNHL and 32% of patients of idiopathic hearing loss, and it was negative. She also

was tested for the GJB2 gene sequence and found to be undetectable – Mutations in the GJB2 gene that encodes the protein connexin 26 (CX26) on chromosome 13, a common gene found in childhood hearing loss. She had several CT scans done of her inner ear, and she recalls being told she had malformation in her inner ear bilaterally, which she was told by her otolaryngologist that the malformation was the cause of her hearing loss and that there may be “something to do with my thyroid gland”. However, she was not told specifically what that association could be.

She did not yet have a diagnosis at the time she presented to endocrine for evaluation of increasing left thyroid gland despite adequate thyroid replacement. She reported that her left thyroid gland was at least 2 times the size of what it was 12 years before when she had her right thyroidectomy. One year before, an ultrasound guided fine needle aspiration of the left gland nodule, which was 3.0 cm in the largest dimension was “benign” at an outside hospital. A repeat in-office ultrasound confirmed a left thyroid nodule measuring 3.7 cm with associated internal vascularity and punctuate calcifications not seen previously. Cytology showed features consistent with chronic lymphocytic Hashimoto's thyroiditis.

Patient returns 3-months after her last ultrasound guided fine needle aspiration with concerns that her goiter will continue to grow and the potential for thyroid cancer. She had returned to the hearing institute, and after discussing her thyroid evaluation with her otolaryngologist, she was told she may have a condition that is related to both. No additional testing was done, and patient was told to return to clinic for routine follow up. I requested that the hearing specialist test her for Pendred syndrome, characterized by bilateral sensorineural hearing loss and thyroid goiter, by testing for the gene *SLC26A4* (solute carrier family 26, member 4 gene), located on chromosome 7 (7q31) (1). The test came back positive for both alleles of the syndrome.

On visual inspection of her neck, she has a low lying 4 centimeter incision scar slightly above her right clavicle, located mostly to the right of midline. The scar was flat and faint. Her thyroid gland is absent on palpation of the right neck, but her left gland is enlarged about two-times normal. The left lower lobe nodule was nearly 4 cm in size. This nodule is soft, mobile upon swallowing, and non-tender. Her cardiac exam is unremarkable. She has no eye findings of exophthalmus or lid lag.

Her vitals are unremarkable and she is wearing bilateral hearing aids. After removing her hearing aids, auditory canals are clear with intact tympanic membranes bilaterally.

The patient's thyroid hormone replacement dose has increased over time from the initial post-surgical dose of levothyroxine 50mcg daily to the present day dose of levothyroxine 150mcg daily. Her current TSH is 2.2. Clinically, the patient appears euthyroid. Her most recent dose adjustment was six months ago when she was on levothyroxine 137mcg daily. It appears she has had an increase in dosing every six months to reach an average TSH range of 1.0-3.0. Her dose has continued to be increased despite taking medication fasting in the morning, an hour before breakfast, and avoiding interfering medication and vitamins for at least four hours after taking her levothyroxine.

### ***Case Discussion***

Pendred syndrome is characterized by clinical presentation of bilateral sensorineural hearing loss and a thyroid goiter, as well as a partial defect in the iodide organification.<sup>2</sup> Pendred syndrome is one of the most common forms of syndromic deafness. It is an autosomal recessive disorder caused by biallelic mutations in the SLC26A4 gene (also called the PDS gene), that encodes for pendrin.<sup>1</sup> Pendrin is a multifunctional anion exchanger that primarily is found in the thyroid gland, the inner ear, and the kidney. In the inner ear, pendrin is important for the creation of normal endolymph compositions and the maintenance of of endocochlear potential. While in the thyroid gland, pendrin is localized to the apical membranes of thyrocytes; with a defect in the SLC26A4 gene a partial iodide organification defect occurs presumed by researchers to be due to a reduced iodide efflux into the follicular lumen.<sup>2</sup> In the kidneys, pendrin is expressed in the cortical collecting duct and thought to be involved in regulation of electrolyte homeostasis along with blood pressure control by mediating net acid and chloride excretion. This may possibly be a target for potential treatment of hypertension.<sup>3,4</sup> However, kidney pendrin defects are not noticed in patients with Pendred syndrome as they typically have normal renal function and do not display any acid-base abnormalities. This suggests that, in these patients, there must be some other chloride-base exchangers that are compensating for the pendrin loss when SLC26A4 gene is defective.<sup>2</sup>

This patient had specific concern about risk for thyroid cancer. In Pendred syndrome, the incidence of thyroid cancer is estimated to be 1%, with the most common form of thyroid cancer being follicular carcinomas.<sup>5</sup> The normal role of pendrin in the apical surface of thyroid cells is that of chloride-iodide transportation. The formation of thyroid hormone involves iodine being transported by pendrin via its chloride-iodide transporter from the cell to the colloid (the protein in the thyroid gland) located in the follicular cell lumen. There, the iodine will bind to tyrosine kinase residues of thyroglobulin and form thyroid hormone. Losing pendrin function would lead to a defect of organification and can lead to a dyshormonogenetic goiter that cannot produce normal thyroid hormone. Constant stimulation by thyroid stimulating hormone (TSH), released from the pituitary in response to low levels of circulating thyroid hormone in the blood, can lead to malignant transformation of these goiters.

Generally, if thyroid cancer does develop, it tends to be follicular thyroid carcinoma, though some reports of papillary thyroid cancer have been noted in the literature, including a case with Pendred identical twins. In this case, one of the twins had papillary thyroid cancer and the other had follicular thyroid cancer.<sup>5</sup> In our case, the patient also the elevation in anti-TPO antibody elevation, which in itself does pose a higher risk of thyroid cancer than patients without anti-TPO antibodies.

This case is further complicated by the patient having both Pendred syndrome and Hashimoto's thyroiditis, or autoimmune thyroid disease. Pendred goiter may not necessarily be present at birth as in our patient who did not exhibit signs of a goiter until later in life. The goiters tend to increase in size despite being on thyroid replacement. Our patient was not on thyroid replacement until after her right thyroidectomy. Her left thyroid continued to grow despite adequate thyroid hormone replacement. Though Pendred syndrome is rare, it often overlaps with other thyroid disorders, such as Hashimoto's thyroiditis, which could leave it undiagnosed for a while unless someone connects the thyroid goiter problem with the hearing loss at a young age.<sup>6</sup>

Prior to the availability of gene mutation analysis, the perchlorate discharge test was considered the best modality to assess for Pendred syndrome. Our patient did not receive this test, as her clinical presentation and the presence of the biallelic involvement of the SLC26A4 gene mutation established the diagnosis.

The perchlorate discharge test involves the following:

1. Radioactive iodine is given to the patient;
2. Time is allowed for the iodine to be captured by the thyroid; and
3. Oral perchlorate is administered.

Patients with Pendred syndrome show an abnormally rapid loss of radioactive iodine from the thyroid. However, false negatives can also occur in patients with Pendred syndrome, as evident in a study of two consanguineous large families in Southern Tunisia. These families had 11 individuals that had thyroid goiters who tested positive for the gene mutation, but had normal perchlorate discharge test result.<sup>7</sup> Of note, the perchlorate discharge test can have similar results in Hashimoto's thyroiditis.

Looking for cochlear malformations, which may not manifest in all Pendred patients, with CT or MRI can help further differentiate between pure Hashimoto's thyroiditis and Pendred syndrome. A CT finding characteristic of Pendred syndrome would be an isolated enlarged vestibular aqueduct or a cochlear malformation called Mondini dysplasia.<sup>8</sup>

In conclusion, there is no effective way of preventing goiter formation in patients with Pendred syndrome. Close follow up, keeping TSH in the normal range, can help. But, in the case of many patients with Pendred syndrome, including our patient, the goiter continues to grow despite adequate replacement of thyroid hormone. Surgical removal of the goiter should be considered if patients develop dysphagia or are noted to have tracheal narrowing. If patients do not require surgery, they are

counseled about their risk of thyroid cancer (the risk being 1%) and the need for regular clinical as well as sonographic monitoring. As with any thyroid nodules, changes in size or character, including presence of vascularity or calcifications, may warrant fine needle aspiration to rule out a thyroid cancer. Pendred syndrome should be considered in any young patient who presents with a history of bilateral hearing loss and thyroid goiter- despite evidence of other possible causes of goiter, such as Hashimoto's or iodine deficiency.

## REFERENCES

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