

Concurrence of Pendred Syndrome, Autoimmune Thyroiditis, and Simple Goiter in One Family

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ABSTRACT

Pendred syndrome is the autosomal recessively transmitted association of familial goiter and congenital deafness. There is no specific biochemical marker of this disease, and the diagnosis depends upon the demonstration of the triad of congenital sensorineural hearing loss, goiter, and abnormal perchlorate discharge test. Pendred syndrome is caused by mutations within the putative ion transporter gene (PDS gene), located on chromosome 7q. A wide variation in the clinical presentation of this condition, and its well documented phe-

notypic overlap with other thyroid disorders (such as Hashimoto's thyroiditis), can lead to diagnostic difficulties. The potential for misdiagnosis increases when these disorders occur coincidentally in the same family. We describe a kindred in which Pendred syndrome, autoimmune thyroiditis, and simple goiter coexisted, to highlight these diagnostic pitfalls and to illustrate the use of mutational analysis in resolving diagnostic confusion. (*J Clin Endocrinol Metab* **84**: 2736–2738, 1999)

PENDRED SYNDROME is the autosomal recessively transmitted association of familial goiter and congenital deafness (1). It is characterized by a partial defect of organification of iodide into thyroglobulin in the thyroid gland and abnormal discharge of unincorporated iodide on the administration of perchlorate (2). Goiters in Pendred syndrome may be present at birth but typically develop in late childhood and may vary significantly in size (3, 4). Indeed, the overall prevalence of goiter in this condition remains unsure, one recent paper identifying goiter in only 73% of familial cases (5). Goiters tend to variably increase in size with time, often despite the oral T₄ therapy (5, 6). Pendred syndrome is one of the most common forms of inherited childhood deafness and has been estimated to be responsible for as much as 7.5% of all congenital deafness (3). Deafness is sensorineural and usually evident at birth, although it may not be recognized for several years. It is variably associated with bilateral malformation of the cochlea (Mondini defect), consisting of absence of the terminal half-coil of cochlea (7, 8), but a much more frequent finding is dilated vestibular aqueduct (9). Defective vestibular function is seen in about 66% of the cases (5). The patients with Pendred syndrome are generally euthyroid, although hypothyroidism can occur (6). The gene for Pendred syndrome (PDS gene) was localized on chromosome 7q by genetic linkage studies (10, 11) and was subsequently identified by positional cloning (12). The PDS

gene encodes a putative ion transporter, called Pendrin. Several common mutations of this gene causing Pendred syndrome have recently been identified, making molecular diagnosis of this condition possible (12–14).

Although Pendred syndrome is a rare condition, with an estimated incidence of 8 in 100,000 (3), other thyroid disorders with goiters, such as simple goiter and autoimmune thyroiditis, are relatively common in the population (15). Therefore, although rare, these disorders can coexist in one family. The phenotypic overlaps between these disorders are well known to cause diagnostic difficulties (16–18); however, the potential for misdiagnosis further increases if these disorders occur coincidentally in the same family, as we describe in this report. In addition, we illustrate the application of mutational analysis in resolving such diagnostic difficulties.

Subjects and Methods

Case reports

Two siblings (subjects III.2 and III.3, of the kindred shown in Fig. 1) have been deaf since birth. Subject III.2 developed a smooth goiter at the age of 11 yr. Thyroid function tests showed mild hypothyroidism, with a free T₄ (FT₄) level of 10.3 pmol/L (normal, 11.7–28) and TSH of 12.8 mU/L (normal, 0.25–4.3). She was started on T₄ replacement. Her younger brother, subject III.3, developed a smooth goiter at the age of 10 yr. At the age of 14 yr, when the goiter size increased significantly and thyroid function tests showed an FT₄ level of 10.1 pmol/L and TSH of 4.8 mU/L, he was also started on T₄. Since diagnosis, goiter size has continued to increase in both patients, and increasing doses of T₄ have been necessary. Thyroid microsomal and thyroglobulin antibodies were negative in both. Serum thyroglobulin measured in subject III.2 was within the normal range, at 29 mg/L (normal, 12–30). Karyotypic analyses were normal (46XX and 46XY, respectively). Further investigations in both siblings strongly supported an underlying diagnosis of Pendred

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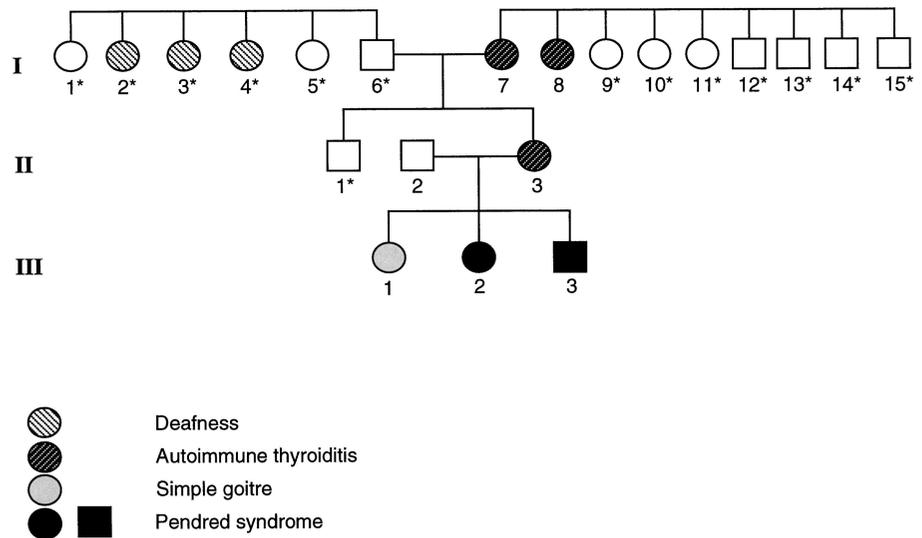


FIG. 1. Pedigree of the kindred, showing Pendred syndrome, autoimmune thyroiditis, and simple goiter in one family. *, Subjects not available for assessment.

syndrome. Perchlorate discharge tests were performed off oral T₄ treatment; T₄ was substituted to T₃, 8 weeks before the test, which was stopped 2 weeks before the test. These tests were positive in both, with 50% and 58% iodine discharge in subject III.2 and subject III.3, respectively (normal, <10%). Pure-tone audiometry in both siblings revealed bilaterally asymmetrical severe-to-profound sensorineural deafness. Vestibular function, assessed with caloric testing and electronystagmography, was normal in subject III.2 but showed a decreased caloric response, on the left side, in subject III.3, indicating impaired vestibular function. Computed tomograms revealed bilateral malformation of the inner ear, typical of Pendred syndrome, in both siblings. Both had dilated vestibular aqueducts (subject III.2, 1.5 mm right and 2.7 mm left; subject III.3, 3.5 mm bilaterally; normal, <1 mm), and subject III.3 additionally showed deficiency of the interscalar septum on both sides, indicating a mild Mondini malformation. Both siblings had normal growth and development and have normal intelligence.

After the diagnosis of Pendred syndrome in the siblings, it was found that their 15-yr-old elder sister (subject III.1) also had a moderate-sized smooth diffuse goiter. She had no history of deafness, and her audiogram was normal. Thyroid function test results were within normal ranges, with an FT₄ level of 14.7 pmol/L, and TSH of 3.9 mU/L. Thyroid autoantibodies were negative. However, in view of her moderate-sized goiter, she was started on T₄ (50 µg/daily). The absence of a hearing deficit, combined with normal perchlorate discharge test results, made the diagnosis of Pendred syndrome unlikely. Needle biopsy of the thyroid gland showed abundant colloid with several sheets of thyroid epithelial cells, an appearance suggestive of colloid goiter. There was no histological evidence of Hashimoto's thyroiditis. When she was reassessed, at the age of 22 yr, it was noted that her goiter had regressed and thyroid autoantibodies continued to be negative. She remained clinically and biochemically euthyroid after stopping T₄ for 8 weeks; therefore, it was discontinued.

There was no history of deafness or thyroid disorder in the father (subject II.2) of the probandi and his family line; however, their mother (subject II.3) has been on T₄ for many years. She initially presented, at the age of 34 yr, with symptoms suggestive of hypothyroidism, which was confirmed by thyroid function tests showing an FT₄ level of 9.3 pmol/L and TSH of 11.9 mU/L. There was no palpable goiter, and she had normal hearing. Her perchlorate discharge test was positive, with 20% iodine discharge. However, she had thyroglobulin and microsomal autoantibodies (1:800 and 1:1600 titers, respectively), consistent with the diagnosis of autoimmune thyroiditis. Her mother and one of her maternal aunts (subjects I.7 and I.8) were also found to have been on T₄ for antibody-positive hypothyroidism. They too had no goiter, and their hearing was normal. Her three paternal aunts (subjects I.2, I.3, and I.4) were known to have been deaf, although the exact etiology is unknown, and were not available for investigation.

Segregation of the PDS gene mutation in the family

Methods. A donor splice site mutation, 1001 + 1G→A, in exon 8 of the PDS gene has been identified in the siblings with Pendred syndrome (subjects III.2 and III.3) (13). Segregation of the mutation in the family was analyzed using the Fok I restriction enzyme, whose site is gained in the presence of this mutation. PCR was carried out, using previously referenced (13) PDS8 primers under standard conditions for 35 cycles at 50 C, on a Peltier thermal cycler (MJ Research, Inc., Watertown, MA). One hundred nanograms of template DNA was amplified, using 37.5 ng of each primer, in a 25-µL reaction, with 1.25 U Taq polymerase (PE Applied Biosystems, Epsom, UK) and 200 µmol deoxynucleotide triphosphates. This was buffered with 100 mmol Tris-HCl and 100 mmol KCl and 1 mmol MgCl₂. Five microliters of product was checked on a 1.5% Seakem LE agarose gel (FMC Bioproducts, Lichfield, UK), before setting up digests on 15 µL of product using 10 U Fok I (New England Biolabs, Inc.) and 7 U HincII (Life Technologies, Paisley, UK) in 1× NEB4 buffer at 37 C for 3 h. Digested products were then separated on a 4% Metaphor gel (FMC BioProducts). The normal 211-bp band is digested into the bands of 174 bp and 37 bp in the presence of the mutation (Fig. 2). All studies were carried out with the approval of the ethics committee.

Results

The affected sibs (subjects III.2 and III.3) were found to be homozygous for the mutation, whereas their elder sister (subject III.1) and both parents (subjects II.2 and II.3) were heterozygous (Fig. 2). These results support the clinical diagnosis of autoimmune thyroiditis and simple goiter, rather than Pendred syndrome, in their mother and elder sister, respectively.

Discussion

The diagnosis of Pendred syndrome is important because of its implications, both for patient management and for genetic counseling of the patients and their families. There is no specific biochemical marker of the disease, and the diagnosis depends on the demonstration of the triad of congenital perceptible hearing loss, goiter, and abnormal perchlorate discharge test, although phenocopies are well recognized (17, 18). Atypical cases of Pendred syndrome have also been reported (16, 19, 20). Even within sibships, goiters vary considerably in size and may even

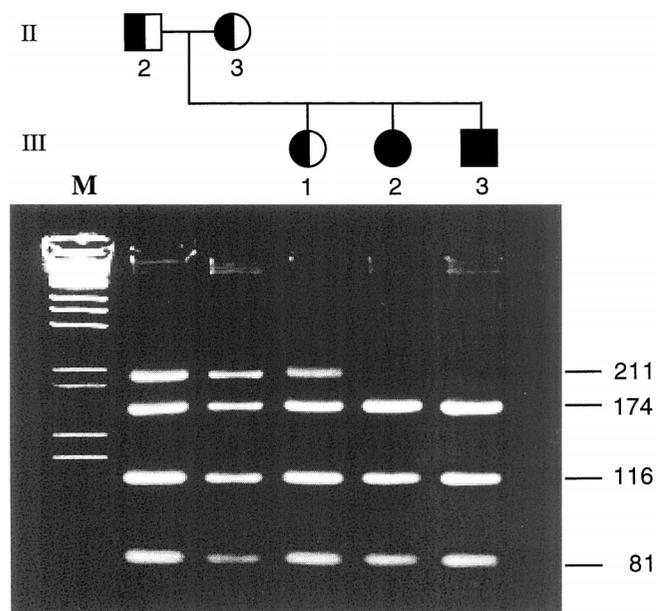


FIG. 2. Segregation of 1001 + 1G→A mutation. Mutation analysis was carried out in the affected sibs, elder sister, and both parents, using *FokI* restriction enzyme. 1001 + 1G→A mutation introduces an additional *FokI* site, restricting the normal 211-bp fragment into bands of 174 bp and 37 bp (too small to be resolved on agarose). The 408-bp PCR product is normally cut into two bands of 211 bp and 197 bp by *FokI*, which proved difficult to resolve. Hence, *HincII* was included in the digests, because this cuts the 197-bp band into two bands of 116 bp and 81 bp. The affected sibs (subjects III.2 and III.3) are homozygous for the mutation, whereas their elder sister (subject III.1) and both parents (subjects II.2 and II.3) are heterozygous. M, Molecular size standard, which is the 1-kb DNA ladder (Life Technologies).

be absent (5). Similarly, the deafness may be only partial or much more severe on one side than the other. On the other hand, Hashimoto's thyroiditis (goitrous autoimmune thyroiditis) can mimic Pendred syndrome in clinical presentation, especially if associated with hearing impairment. Hashimoto's thyroiditis, like Pendred syndrome, is known to occur in several members of the same family (21). The perchlorate discharge test, which is regarded as the hallmark of Pendred syndrome, can also be positive in Hashimoto's thyroiditis (17, 18, 22, 23), whereas false negative results in Pendred syndrome have been reported (5). Furthermore, thyroid autoantibodies can be present coincidentally in patients with Pendred syndrome (6) and, very occasionally, be absent in Hashimoto's thyroiditis (24). The cochlear malformations, on computed tomography scan and magnetic resonance imaging, are not specific to Pendred syndrome but would not be expected to be present in Hashimoto's thyroiditis with or without hearing impairment. However, up to 10% of Pendred syndrome cases have normal radiology of the cochlea (9). Hence, radiological features cannot be relied on to differentiate between these two eventualities. Similarly, differentiating sporadic goiter from Pendred syndrome can also sometimes be difficult (16).

The absence of a single readily available diagnostic test for Pendred syndrome, combined with the well-documented phenotypic overlap with other thyroid disorders, can make for diagnostic difficulties. The family that we present highlights these diagnostic pitfalls and emphasizes the need for open-mindedness in approaching families with a vague history of

thyroid disease. Subject II.3 (Fig. 1) of our kindred was diagnosed as having autoimmune thyroiditis, in spite of a positive perchlorate discharge test, on the basis of the clinical presentation, positive thyroid autoantibodies, and presence of autoimmune thyroiditis in other family members. In subject III.1, Pendred syndrome and Hashimoto's disease were excluded, based on the clinical features, normal perchlorate discharge test, negative thyroid autoantibodies, and thyroid biopsy. Mutational analysis has helped to confirm and exclude the diagnosis of Pendred syndrome in the family members. This family demonstrates that the diagnosis of Pendred syndrome is firmly rooted in an overall consideration of the clinical features, the family history, and the interpretation of complex radiological and thyroid investigations, relative to one another. With recent identification of the common PDS gene mutations (12–14), the molecular diagnosis of Pendred syndrome has become possible, which should ease the scope for diagnostic confusion.

References

- Pendred V. 1896 Deaf mutism and goitre. *Lancet*. 2:532.
- Morgans ME, Trotter WR. 1958 Association of congenital deafness with goitre. The nature of the thyroid defect. *Lancet*. 1:607–609.
- Fraser GR. 1965 Association of congenital deafness with goitre (Pendred's syndrome); a study of 207 families. *Ann Hum Genet*. 28:201–249.
- Illum P, Kiaer HW, Hvidberg-Hansen J, Sondergaard G. 1972 Fifteen cases of Pendred's syndrome. *Arch Otolaryngol (Stockholm)*. 96:297–304.
- Reardon W, Coffey R, Phelps PD, et al. 1997 Pendred syndrome - 100 years of underascertainment? *Q J Med*. 90:443–447.
- Friis J, Johnsen T, Feldt-Rasmussen V, Beck K, Friis T. 1988 Thyroid function in patients with Pendred syndrome. *J Endocrinol Invest*. 11:97–101.
- Hvidberg-Hansen J, Balslev Jorgensen M. 1968 The inner ear in Pendred's syndrome. *Acta Otolaryngol (Stockholm)*. 66:129–135.
- Johnsen T, Larsen C, Friis J, Hougaard-Jensen F. 1987 Pendred syndrome-acoustic, vestibular and radiological findings in 17 unrelated patients. *J Laryngol Otol*. 101:1187–1192.
- Phelps PD, Coffey RA, Trembath RC, et al. 1998 Radiological malformations of the ear in Pendred syndrome. *Clin Radiol*. 53:268–273.
- Coyle B, Coffey R, Armour JAL, et al. 1996 Pendred syndrome (goitre and sensorineural hearing loss) maps to chromosome 7 in the region containing the nonsyndromic deafness gene DFNB4. *Nat Genet*. 12:421–423.
- Sheffield VC, Kraiem Z, Beck J, et al. 1996 Pendred syndrome maps to chromosome 7q21–34 and is caused by an intrinsic defect in thyroid organification. *Nat Genet*. 12:424–426.
- Everett LA, Glaser B, Beck JC, et al. 1997 Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). *Nat Genet*. 17:411–422.
- Coyle B, Reardon W, Herbrick J, et al. 1998 Molecular analysis of the PDS gene in Pendred syndrome (sensorineural hearing loss and goitre). *Hum Mol Genet*. 7:1105–1112.
- Van Hauwe P, Everett LA, Coucke P, et al. 1998 Two frequent missense mutations in Pendred syndrome. *Hum Mol Genet*. 7:1099–1104.
- Tunbridge WMG, Evered DC, Hall R, et al. 1977 The spectrum of thyroid disease in a community: the Wickham survey. *Clin Endocrinol (Oxf)*. 7:481–493.
- Bax GM. 1966 Typical and atypical cases of Pendred's syndrome in one family. *Acta Endocrinol (Copenh)*. 53:264–270.
- O'Mahoney CF, Luxon LM, Chew SL, Wass JAH. 1996 When the triad of congenital hearing loss, goitre and perchlorate positive is not Pendred syndrome. *J Audiol Med*. 5:157–165.
- Reardon W, Coffey R, Pembrey ME, et al. 1997 Pitfalls in practice - diagnosis and misdiagnosis in Pendred syndrome. *J Audiol Med*. 6:1–9.
- Johnsen T, Sorensen MS, Feldt-Rasmussen U, Friis J. 1989 The variable intrafamilial expressivity in Pendred's syndrome. *Clin Otolaryngol Allied Sci*. 14:395–399.
- Jamal MN, Arnout MA, Jarrar R. 1995 Pendred's syndrome: a study of patients and relatives. *Ann Otol Rhinol Laryngol*. 104:957–962.
- Hall R, Stanbury JB. 1967 Familial studies of autoimmune thyroiditis. *Clin Exp Immunol*. 2:719–725.
- Morgans ME, Trotter WR. 1957 Defective organic binding of iodine by the thyroid in Hashimoto's thyroiditis. *Lancet*. 1:553–555.
- Takeuchi K, Suzuki H, Horiuchi Y, Mashimo K. 1970 Significance of iodide-perchlorate discharge test for detection of iodine organification defect of the thyroid. *J Clin Endocrinol Metab*. 31:144–146.
- Loeb PB, Drash AL, Kenny FM. 1973 Prevalence of low titer and 'negative' anti-thyroglobulin antibodies in biopsy-proved juvenile Hashimoto's thyroiditis. *J Pediatr*. 82:17–21.