**Pendred syndrome** consists of the combination of hearing impairment and euthyroid or hypothyroid goiter (1). Although this disease was described more than a hundred years ago, it remains unknown to most physicians in clinical practice, and its diagnosis is certainly often missed (2). A possible reason for this situation is the highly variable course of both the hearing impairment and the thyroid dysfunction. Though only about 10 families with Pendred syndrome have been identified in Germany in the literature published to date (3–6), it seems highly likely that there are more persons with this disease in Germany who would benefit from early diagnosis and treatment. Interestingly, two major clinical manifestations of Pendred syndrome, congenital hypothyroidism (frequency 1 : 4 000) and congenital hearing impairment (frequency approximately 1 to 2 : 2 000) can now be diagnosed in the neonatal period (7,8).

The purpose of this review article is to describe the relevant considerations of diagnosis and treatment of this disease for physicians in clinical practice, while also discussing its molecular genetic and pathophysiological aspects.

**Methods**

This article is based upon published papers retrieved by a Medline search, which was last performed in January 2006, on the terms "Pendred," "Pendred's," or "SLC26A4," and "mutation." Pendred syndrome is caused by mutations in the SLC26A4 gene. It is a common cause of syndromic deafness as well as the second commonest cause of isolated deafness. Clinical genetic diagnosis allows identification of SLC26A4 mutations. Discussion: Despite being a common cause of congenital deafness, Pendred syndrome is probably underdiagnosed in Germany. Molecular analysis and thorough clinical assessment can confirm the diagnosis of Pendred syndrome. Treatment is largely symptomatic, and aims to optimize hearing and language development.


Key words: Pendred syndrome, deafness, hypothyroidism, goiter, molecular genetics

Pendred syndrome consists of the combination of hearing impairment and euthyroid or hypothyroid goiter (1). Although this disease was described more than a hundred years ago, it remains unknown to most physicians in clinical practice, and its diagnosis is certainly often missed (2). A possible reason for this situation is the highly variable course of both the hearing impairment and the thyroid dysfunction. Though only about 10 families with Pendred syndrome have been identified in Germany in the literature published to date (3–6), it seems highly likely that there are more persons with this disease in Germany who would benefit from early diagnosis and treatment. Interestingly, two major clinical manifestations of Pendred syndrome, congenital hypothyroidism (frequency 1 : 4 000) and congenital hearing impairment (frequency approximately 1 to 2 : 2 000) can now be diagnosed in the neonatal period (7,8).

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**Pendred syndrome – definition and clinical features**

Pendred syndrome is inherited in an autosomal recessive pattern. Patients with the disease have disease-producing mutations in both copies of the relevant gene, while both parents are phenotypically normal, heterozygous carriers. Any child born to a pair of heterozygous carriers, whether male or female, has a 25% chance of having the disease.

Pendred syndrome was first described in 1896 by the British general practitioner Vaughan Pendred (1869–1946) (9). Its leading manifestation is hearing impairment, which is always bilateral, although one ear may be more severely affected than the other (10). The hearing impairment is of the sensorineural type and is usually severe, with a magnitude of at least...
Types of progression of hearing impairment in Pendred syndrome. The course of hearing impairment is shown for three patients, all siblings, who were homozygous for the identical mutation, designated T416P. A representative selection of audiograms is displayed for each of the three siblings over a 23-year course. To facilitate comparison, audiograms obtained at different ages are superimposed on each other in the same graph. The graph on the left for each patient represents the right ear, and vice versa. For Patients 1 and 2, the first audiogram (red) was a free-field reaction audiogram and appears on the left side of the figure. All of the other audiograms displayed here were pure-tone audiograms obtained from the two ears separately. Hearing impairment took a variable course in these three patients despite their common genotype: it was severe and progressive in Patient 1, severe but not progressive in Patient 2, and least severe initially, but with later, marked worsening, in Patient 3. Figure from Napiontek et al. (5). Copyright 2004, The Endocrine Society. Reprinted with permission.
60 decibels (dB). It is usually already present at birth and thus typically comes to medical attention through the absence or marked delay of language development (so-called prelingual hearing impairment). In rare cases, an affected child may undergo normal or only mildly delayed language development, so that the hearing impairment is not diagnosed till early childhood or even later. The hearing impairment of Pendred syndrome involves all frequencies, but the higher frequencies are usually more severely affected (diagram 1). The course of the hearing impairment is variable. It tends to take one of the following three forms:

1. The hearing impairment remains stable for several years
2. It fluctuates in severity, with episodes of sudden worsening and of partial or complete remission
3. It progresses in severity, ending as bilateral deafness.

The cause of this phenotypic variability has not yet been determined. It has been found that the hearing impairment may take a different course in two affected siblings with identical molecular genetic defects (diagram 1).

In addition to hearing impairment, the other characteristic feature of Pendred syndrome is thyroid involvement, with goiter and hypothyroidism (1, 11). A defect of thyroid hormone synthesis impairs the transport of iodide from thyroid cells into the colloid. Unlike the hearing impairment, which is always present, the thyroid abnormality is of highly variable severity, especially in children; it may be absent when the hearing impairment is first diagnosed. Although neonates with Pendred syndrome rarely have an enlarged thyroid gland, approximately 75% of affected persons will eventually develop a multinodular or diffuse goiter (11). Sometimes the goiter must be surgically resected at some point in the course of the disease because of tracheal compression. It remains unknown why the goiter often does not appear till late childhood, adolescence, or early adulthood.

**Diagnostic evaluation**

Pendred syndrome is diagnosed on clinical grounds alone, because no simple laboratory test for the disease is available. The diagnosis of Pendred syndrome should be considered in all patients suffering from a bilateral sensorineural deafness in combination with goiter, hypothyroidism, or hypothyroid goiter.
Figure
An enlarged vestibular aqueduct: the typical inner ear malformation associated with Pendred syndrome. Neuroradiological depictions of bilateral enlarged vestibular aqueducts (EVAs) in patients with Pendred syndrome: high-resolution CT (a, b) and MRI (c, d). The arrows point to enlargements in the vestibular aqueducts. The star in (d) indicates an additional ampullary cyst in the cerebellopontine angle. Figure from Napiontek et al. (5). Copyright 2004, The Endocrine Society. Reprinted with permission.
hypothyroidism, and/or a congenital anomaly of the inner ear (see box). Precise history-taking and meticulous physical examination are essential if the diagnosis is not to be missed. An extensive family history should be elicited, because, as in other autosomal recessive forms of congenital deafness, the diagnosis is more likely if the parents are consanguineous or if one or more siblings are already known to be affected. The child’s hearing, language skills, and psychomotor development should also be taken into account. If the child has an enlarged thyroid gland or manifestations of hypothyroidism, further studies should be performed, in a manner appropriate to his or her age and developmental level. These include both subjective audiometric testing (reflex, reaction, pure tone, and speech audiometry) and electrophysiological testing to determine the auditory threshold, e.g., the measurement of otoacoustic emissions and the recording of brainstem auditory evoked potentials. Nearly all patients with Pendred syndrome have a congenital inner ear anomaly (12).

High-resolution imaging of the petrous bones with computed tomography (CT) or magnetic resonance tomography (MRT) reveals an enlarged vestibular aqueduct (EVA) in 85% to 100% of cases (figure a–d). Approximately 20% of all patients also have an anomalously formed, hypoplastic cochlea, the so-called Mondini deformity. The presence of an EVA in a hearing-impaired child should always lead to the inclusion of Pendred syndrome in the differential diagnosis, even though EVA is the most common neuroradiological finding in children with sensorineural hearing impairment and is not specific for Pendred syndrome. Nor has any correlation been demonstrated to date between the presence and extent of an EVA and the severity of hearing impairment.

If Pendred syndrome is suspected on clinical grounds, the patient’s thyroid function should be checked. The most important thyroid parameters are the serum concentrations of thyroid-stimulating hormone (TSH) and free thyroxine (fT4) (11). The hypothyroidism associated with Pendred syndrome is of the primary type, i.e., the disturbance of thyroid hormone biosynthesis is located in the thyroid gland itself and is not due to dysfunction of the hypothalamic pituitary axis (11, 13). Thus, the fT4 concentration is low and the TSH concentration is elevated. Newborn infants with Pendred syndrome are often still euthyroid; only a few cases have reported to date in which Pendred syndrome was diagnosed in the neonatal period (11). In some patients, the hypothyroidism is compensated, i.e., the thyroid gland, under the influence of an increased amount of TSH, is still able to produce enough thyroid hormone to sustain a euthyroid metabolic state.

As in other deficiencies of thyroid hormone synthesis, the serum thyroglobulin concentration is often elevated; this may be an important clue to the differential diagnosis.
Finally, thyroid ultrasonography allows a lobe-by-lobe determination of thyroid volume as well as visualization of any cysts that may be present. It facilitates the diagnostic distinction between Pendred syndrome and inflammatory or malignant diseases of the thyroid gland. The available literature provides insufficient information to determine whether the goiter associated with Pendred syndrome is a risk factor for malignant degeneration. It should be mentioned, however, that a small number of cases have been reported in which malignant thyroid tumors arose in goiters of patients with Pendred syndrome (14). This is a further reason why the thyroid gland should be periodically followed up with ultrasonography.

The perchlorate discharge test (PDT) was long considered to be the most important criterion for the diagnosis of Pendred syndrome (1). It is used to demonstrate the presence of an iodide organification defect in the thyroid gland. Radioactively labeled iodine is administered, followed by perchlorate, which displaces iodine, in order to determine whether the thyroid gland fixes iodine adequately. In Pendred syndrome, as in other defects of thyroid hormone synthesis, the test is typically positive, i.e., the thyroid gland does not adequately incorporate the radiolabeled iodine into thyroid hormone molecules.

Until a few years ago, the triad of congenital bilateral sensorineural hearing impairment, goiter, and positive PDT was thought to constitute proof of the diagnosis of Pendred syndrome. The PDT, however, is neither 100% specific nor 100% sensitive, and the great majority of patients and their parents will not allow it to be performed in any case. This test, therefore, is increasingly being replaced by molecular genetic analysis. Molecular diagnosis of Pendred syndrome has been available since 1997 and is based on sequence analysis of the Pendred syndrome gene (PDS/SLC26A4), which can be performed from an EDTA blood sample. If the patient is found to possess two mutations of this gene that are already known to cause disease (homozygote or compound heterozygote), the diagnosis is established. It remains possible, however, that only one mutation will be found, i.e., that the patient will be found to be a heterozygote. In this case, the patient has Pendred syndrome only if the second allele contains a cryptic mutation or deletion, i.e., one that cannot be identified on routine testing. Finally, there are rare, usually sporadic cases of Pendred syndrome in which no mutations are found. This implies that other genetic causes of Pendred syndrome may exist beyond the single Pendred syndrome gene that has been identified to date.

The effective diagnosis and optimal treatment of patients with Pendred syndrome requires the interdisciplinary collaboration of pediatricians, endocrinologists, geneticists, phoniatrists/pediatric audiologists, ENT specialists, and neuroradiologists.

**Differential diagnosis**

The hearing impairment and thyroid abnormalities of Pendred syndrome each have their own differential diagnosis, as will be discussed in this section. Hearing impairment and goiter are common problems in themselves, and their joint appearance in a single patient does not necessarily imply the presence of Pendred syndrome.

If a patient suffers from hearing impairment of unknown etiology, non-genetic causes should be excluded first (15). These include intrauterine infection (e.g., toxoplasmosis, rubella, and cytomegalovirus infection), premature birth, perinatal asphyxia, and the ototoxic side effects of postnatally administered medications, particularly aminoglycoside antibiotics and cytostatic agents.

Approximately 50% to 60% of all cases of permanent hearing impairment arising in childhood are due to genetic defects (16). There are syndromal forms associated with dysfunction or congenital defects of other organs, as well as non-syndromal (isolated) hearing impairment. An article by Kubisch that previously appeared in this journal dealt with the genetic causes of non-syndromal hearing impairment (17). That article discussed the important role of the connexins, particularly connexin 26, which is the most commonly mutated gene causing hearing impairment (18).

The first task in clinical diagnosis is, therefore, to determine whether the hearing impairment is syndromal or non-syndromal. If goiter or hypothyroidism is found, the possibility of Pendred syndrome should be suspected. If the patient is then determined to have the typical complex of disease manifestations (congenital bilateral hearing impairment with enlarged vestibular aqueduct and goiter or a pathological perchlorate discharge test), the diagnosis of Pendred syndrome is highly likely and molecular genetic testing should be recommended. Mutations of the Pendred syndrome gene, however, are also a common cause
of isolated hearing impairment; thus, the lack of other clinical signs of the disease does not rule out this diagnosis.

Pendred syndrome may also be diagnosed from the other direction, i.e., in a child who initially comes to medical attention because of thyroid abnormalities, which may be of highly variable severity. The differential diagnostic considerations in this situation are as follows.

The commonest cause of goiter worldwide is iodine deficiency (7). In a child with goiter, other disturbances of thyroid hormone synthesis should also be included in the differential diagnosis, as well as inflammatory and malignant diseases of the thyroid gland. Pendred syndrome is sometimes hard to distinguish from other causes of disturbed thyroid hormone synthesis, but most of these other causes are not associated with deafness (19). If an inflammatory or malignant disease of the thyroid gland is present, then further laboratory tests are required (e.g., antithyroid antibodies, tumor markers), as well as thyroid ultrasonography and scintigraphy.

Molecular genetics and pathophysiology

Almost exactly 100 years after the first clinical description of Pendred syndrome, the responsible gene for it was found on chromosome 7 – the PDS gene, or SLC26A4, as it is now officially called (26). This gene is expressed in the thyroid gland, the inner ear, and the kidney. The gene product, a protein called pendrin, functions as an iodide transporter from within thyroid cells into the colloid, in which thyroid hormone is synthesized (diagram 2).

Mutations in both alleles of this gene cause Pendred syndrome (3–6, 20). More than 90 mutations in the SLC26A4 gene that cause Pendred syndrome have been identified to date (diagram 3). Only eight of the mutations found in Germany have been published (3–6). One of these mutations, V138F, seems to be more common in Germany than elsewhere (4). In rarer cases, SLC26A4 mutations can also cause isolated hearing impairment with EVA but without thyroid involvement (21).

In vitro studies have shown that goiter in Pendred syndrome is caused by the lack of pendrin protein function. It has been demonstrated that a number of SLC26A4 mutations result in the synthesis of altered pendrin proteins that are abnormally distributed within the thyroid cells. Rather than being incorporated into the cell membrane, where pendrin normally carries out its function, these mutated pendrin molecules remain in the endoplasmic reticulum (22). This leads to a diminished amount of iodide transport into the thyrocolid and thus to diminished T3 and T4 synthesis, hypothyroidism, and goiter.
Treatment
Pendred syndrome is treated symptomatically. The goal of treatment is to enable the hearing and speech of affected children to develop as normally as possible. There have been no controlled studies of treatment, as this is a rare disease. It seems reasonable to assume, however, that the affected children stand to benefit from the early provision of hearing aids and special education. Early diagnosis is very important so that this can be achieved. Regular follow-up testing of audition is recommended so that progressive worsening can be detected, if present, and hearing aids can be accordingly optimized. Finally, for patients with bilateral deafness, cochlear implant surgery is indicated (23).

If hypothyroidism is present, the patient should be treated at once with thyroid hormone substitution to enable normal mental and physical development. This treatment also has a favorable effect on the size of the thyroid gland. Sometimes the size of the thyroid fails to change favorably despite substitution therapy, either because of faulty compliance or for other, unknown reasons. Therefore, close follow-up is required, particularly in adolescent patients.

Summary and future perspectives
Pendred syndrome is a common type of syndromal hearing impairment, and mutations of the SLC26A4 gene are the second most common cause of non-syndromal hearing impairment (24, 25). Molecular genetic analysis enables the identification of SLC26A4 mutations in both alleles of the gene in affected persons, providing conclusive proof of the diagnosis. Early diagnosis is of great importance to the treating physician and the affected patients, so that measures can be taken immediately to enable hearing and language to develop as normally as possible. Early diagnosis is also promoted by attentiveness to children’s hearing and language function on the part of parents and day-care or school personnel. If a problem in these areas is suspected, an audiological examination should be performed. Whenever hearing impairment is documented, the child’s thyroid function should also be tested, so that thyroid hormone substitution, if it is needed, can be begun as soon as possible.

In the future, it would be desirable to have molecular genetic studies that would yield prognostic information about the probable course of the disease and that would enable further improvements in its treatment. To this end, the clinical course of Pendred syndrome should be studied and correlated with the molecular genetic findings in as many patients as possible who suffer from this disease.

Conflict of Interest Statement
The authors declare that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.

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