Diagnosis Protocol and Care

PNDS 2021

Pendred syndrome

This Protocol was led by Dr. Sandrine Marlin

French Genetic Hearing loss Reference Centre

French Reference Centre for Endocrine Diseases of Growth and development

French Reference Centre for Rare Thyroid and Receptor Diseases hormones

French Filière de santé maladies rares Sensory Rare Diseases SENSGENE

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List of abbreviations.

SNHL – Sensorineural Hearing Loss

ERN – European Reference Network

HAS – Haute Autorité de Santé (French National Authority for Health)

ENT – Ear, Nose, and Throat

SLC26A4 – Solute Carrier Family 26 Member 4 (gene associated with Pendred syndrome)

CT – Computed Tomography

MRI – Magnetic Resonance Imaging

ELDS – Bilateral enlargement of the endolymphatic duct and sac

L-thyroxine – Levothyroxine (thyroid hormone treatment)

NGS – Next Generation Sequencing

HGMD – Human Gene Mutation Database

CGH-array – Comparative Genomic Hybridization array

MLPA – Multiplex Ligation-dependent Probe Amplification

BOR – Branchio-Oto-Renal syndrome

DFNB4 – Non-syndromic Deafness type 4 caused by SLC26A4 mutations

ABR – Auditory Brainstem Response

ASSR – Auditory Steady State Response

OAE – Otoacoustic Emissions

VHIT – Video Head Impulse Test

cVEMP – Cervical Vestibular Evoked Myogenic Potentials

oVEMP – Ocular Vestibular Evoked Myogenic Potentials

BMI – Body Mass Index

TSH – Thyroid Stimulating Hormone

FT4 – Free Thyroxine

EU-TIRADS – European Thyroid Imaging Reporting and Data System

LEDS - Large Endolymphatic Duct Syndrome (radiological inner ear finding)

µg/kg/d — Micrograms per kilogram per day (dosage measure)

T3L — Liothyronine (T3 hormone)

mUI/L — milli-International Units per Liter (measure of hormone concentration)

AC-anti-TPO — Anti-Thyroid Peroxidase Antibodies (autoimmune thyroid antibodies)

Summary

Pendred Syndrome is a genetic disease. Its prevalence is estimated at 1-9/100 000.

This syndrome combines two main signs: a SNHL with early onset (congenital) and a goitre. The prognosis is primarily auditory, since the severity of the hearing loss will limit the reception of speech and hinder the appropriation of the oral language, resulting in a social impact.

The first clinical sign is a congenital sensorineural hearing loss with early onset (before 3 years). This is most often bilateral and asymmetric. If it is not a profound hearing loss, the hearing deficit is generally fluctuating and progressive in time. Episodes of sudden worsening can occur at any time. SNHL is systematically associated with a bilateral malformation of the inner ear (including bilateral enlarged vestibule aqueduct) visible on a temporal bones CT or an internal auditory canals MRI. The existence of this malformation of the inner ear during the management of a sensorineural hearing loss makes it possible to suspect the diagnosis of Pendred syndrome before the onset of thyroid signs. Signs of vestibular impairment may be associated in a large number of patients. They will be manifested either in delayed motor acquisition if vestibular dysfunction is congenital and bilateral, or vertigo episodes in case of lateral semicircular canal dysfunction.

Diagnosis and management of hearing and vestibular disorders of young children should be carried out in a pediatric ENT service. The diagnosis is based on objective and subjective age-appropriate hearing tests.

The management of the hearing loss is based on the use of an auditory prosthesis (hearing aids or cochlear implants depending on hearing loss severity), and speech therapy. The management of vestibular disorders combines drug treatments and specific physiotherapy. Due to the progressive nature of the hearing loss, the audiological assessment should be repeated during follow-up, at least annually if the hearing loss is stable or even more frequent depending on the patient’s symptoms.

Thyroid disorders most often occur around adolescence. They are diagnosed by the appearance of an eu- or hypothyroidal goitre or aspecific signs of hypothyroidism. Thyroid dysfunction can also be diagnosed during systematic monitoring of a child with hearing loss due to biallellic SLC26A4 pathogenic variations. In the case of hypothyroidism, treatment is based on oral L-thyroxine, from diagnosis throughout the entire life span. In the absence of compressive signs and nodular pathology, clinical and ultrasound monitoring of goitre may be proposed (1 time/year to paediatric age and 1 time/2 years to adulthood). Thyroidectomy should be avoided, if possible, especially in children, in order to limit the risk of post-operative complications. Its indication and implementation are the responsibility of the expert centres after multi-disciplinary consultation.

The diagnosis of Pendred’s syndrome is confirmed by a genetic analysis requested in case of a SNHL associated to a bilateral enlargement of the endolymphatic ducts/sacs. Biallellic SLC26A4 pathogenic

variations is responsible for almost 100 % of cases of Pendred syndrome, but also for an isolated form of SNHL having the same characteristics without thyroid dysfunction. It is estimated that 10 % of children with biallellic *SLC26A4* pathogenic variations will develop Pendred syndrome. Pendred syndrome is transmitted with an autosomal recessive mode of inheritance. A couple of parents, having a child with Pendred syndrome, has a 25% risk of recurrence during each pregnancy of having another child with Pendred syndrome, be it a boy or a girl.

There are no other known pathologies today associated with Pendred syndrome. No specific medical treatment for Pendred syndrome is currently available. Gene therapy remains limited to research.

The diagnosis and follow up of this syndrome should be organised in a specialised centre or by professionals in collaboration with a specialised centre.

1 Introduction

Pendred Syndrome is a genetic disease. Its prevalence is estimated at 1-9/100 000. This syndrome combines two main signs: congenital or early onset SNHL and a goitre. This syndrome is due to biallellic SLC26A4 pathogenic variations and transmitted with an autosomal recessive mode of inheritance.

2. Purpose and Scope of the ERN supported protocol

This document is a diagnostic and care protocol supported by the European Reference Network (ERN). Its purpose is to inform healthcare professionals about the current best practices for the diagnosis, treatment, and long-term management of patients with Pendred syndrome. The protocol aims to improve and harmonize care for this rare disease across Europe.

The development of this protocol follows the methodological principles outlined in the *Method for the Development of a National Protocol for Diagnosis and Care for Rare Diseases*, published by the French Haute Autorité de Santé (HAS) in 2012 (methodological guide available on the HAS website: www.has-sante.fr). Originally developed in France, the protocol was translated from French into English within the ERN framework, ensuring alignment with recognized standards for rare disease care protocol development.

It is important to note that this document cannot account for all individual clinical scenarios, comorbidities, or local healthcare practices. It is not an exhaustive care plan and does not replace the professional judgment or responsibility of the treating physician. Rather, it provides a framework to support standardized care for patients with Pendred syndrome, which should be adapted to individual clinical contexts.

This protocol will be updated regularly as new validated evidence becomes available.

3. Diagnosis and Initial Assessment

3.1 Objectives

- To make an early diagnosis of Pendred syndrome and organise specialised medical visits during the initial assessment (ENT, endocrinologists, geneticists).
- To organise an age-appropriate hearing loss management.
- To provide appropriate surgical management in case of severe to profound hearing loss.

- To organise long-term monitoring, in particular audiological.
- To inform parents about the different ways and stages of care for their child
- To evaluate thyroid functional impairment of Pendred syndrome.
- To evaluate thyroid morphological impairment of Pendred syndrome.
- To inform about the need for extended thyroid follow-up from childhood to adulthood.
- To inform about the necessity of monitoring thyroid nodules if they exist, similar to the monitoring of thyroid nodules in the general population.
- To provide psychological care for children and their families.
- To propose contact with a patient association.
- To inform about the need for long-term follow-up.

3.2 Professionals involved (and coordination arrangements)

The diagnosis of the disease is the responsibility of specialist doctors: geneticists, ENT and endocrinologists.

Diagnosis, initial evaluation and overall patient management are based on multidisciplinary collaboration and involve:

- Paediatricians or general practitioners: follow-up;
- Oto-rhino-laryngologists: in initial diagnosis, management, and follow-up;
- Endocrinologist or pediatric endocrinologist: initial diagnosis, care, and follow-up;
- Clinical geneticist: initial diagnosis, care, and follow-up;
- Genetics Counsellor: care, and follow-up;
- Radiologists: initial diagnosis;
- Radio-isotopist: diagnosis of thyroid disorders;
- Surgeon: surgical management of the goitre, if necessary;
- Audioprosthesist: adaptation and follow-up of hearing aids;
- Speech therapists specialised in the care of pediatric hearing loss: assessment and rehabilitation of the language in the hearing impaired child, and hearing rehabilitation, either by conventional hearing aid or by cochlear implant;

- Physiotherapists specialised for the management of children’s vestibular disorders or delayed motor development;
- Nurse: initial diagnosis, care and follow-up;
- Psychologists: care and follow-up;
- Social workers: support and follow-up.

All of these professionals work in conjunction with the patient’s reference physician, whether they are pediatric or adult.

3.3 Circumstances of discovery/Suspicion of diagnosis

We can discuss three main circumstances for the discovery of Pendred syndrome:

- Evidence of internal ear malformations including a bilateral enlargement of the endolymphatic duct/sac during the initial radiological check-up in a hearing impaired child;
- The appearance of a goitre or hypothyroidism in a hearing impaired child or young adult;
- The existence of a family history of Pendred syndrome in a hearing impaired child or adult.

The diagnosis will only be confirmed when biallellic SLC26A4 pathogenic variations are confirmed.
Some common clinical features of hearing loss may, however, suggest the possibility of Pendred syndrome:

- Congenital or pre-lingual appearance
- Fluctuating hearing loss
- Episodes of sudden worsening of hearing loss with dizziness and tinnitus
- Association with vestibular symptoms.

Two radiological characteristics are also evocative, especially if they are associated:

- Bilateral ELDS
- Malformation of the cochlea type Mondini: Bilateral ELDS associated with cochlear malformation.

3.4 Confirmation of diagnosis/differential diagnosis

3.4.1 Confirmation of diagnosis

The clinical geneticist sends a sample (blood or saliva) of the patient to the molecular diagnostic laboratory for confirmation of diagnosis by analysis of the *SLC26A4*.

SLC26A4 analysis has been extensively performed since its involvement in Pendred syndrome and isolated deafness called DFNB4.

Sanger sequencing remains the reference method (43 articles), but more and more laboratories perform this analysis using high-throughput sequencing that screens a large number of genes at a time (NGS). It is necessary to study the whole coding sequence of *SLC26A4* and not limit the analysis to the most commonly mutated exons.

The pathogenic variations found are numerous and varied: 600 were listed by HGMD (2025-1 release). In terms of frequency, there are mostly missense or nonsense variations (375 followed by anomalies in canonical splice sites (81), small deletions, insertions or indels (deletion/insertion). 13 major deletions and two complex rearrangements were described.

Since Pendred syndrome is transmitted with an autosomal recessive mode (Appendix 4), the diagnosis can only be confirmed by the identification of pathogenic variations of the two copies of this gene in the patient.

However, the number of patients with bilateral ELDS carrying only one *SLC26A4* pathogenic variation, is larger than expected in the general population. Several unconfirmed hypotheses have been put forward to explain this observation:

- Pathogenic variations in the promoting region, in particular at FOXI transcription factor fixation sites.
- A digenic inheritance with a pathogenic variation of the FOXI1 gene in trans (on the other allele) of a *SLC26A4* pathogenic variation.
- A digenic inheritance with a pathogenic variation of the KCNJ10 *gene* in trans of a *SLC26A4* pathogenic variation.
- Presence of large trans *SLC26A4* rearrangements; can be identified by CGH-array or MLPA.
- Existence of a haplotype (of the name CEVA) common to many families, suggesting that another recurrent anomaly remains to cover (deep intronic pathogenic variation, in non coding regions...) in trans of a *SLC26A4* pathogenic variation.

Once the molecular diagnosis has been established for the index case, genetic testing in both parents is recommended to verify the segregation of pathogenic variations.

Subsequently, a molecular study of the relatives at risk of carrying one or two *SLC26A4* pathogenic variations could be proposed.

3.4.2 Differential diagnosis

There are no other known pathology today associating all the signs of Pendred syndrome: SNHL, bilateral ELDS and thyroid goitre.

SNHL with ELDS can be found in other genetic syndromes, associated with other clinical signs, which are not found in Pendred syndrome, such as BOR, Kabuki, BOF and Down syndromes or Deafness and Tubular Acidosis.
On the other hand, there are other genetic syndromes combining hearing loss and thyroid pathology but without malformation of the inner ear and with many other clinical signs (Wolfram Syndrome, Alström syndrome).

Biallellic SLC26A4 pathogenic variations are responsible for almost 100 % of cases of Pendred syndrome but also an isolated form of deafness with the same characteristics, without thyroid dysfunction (DFNB4). It is estimated that 10 % of children with bilallelic SLC26A4 pathogenic variations will develop Pendred syndrome.

Since the existence of a neonatal goitre or congenital hypothyroidism as part of a Pendred syndrome is exceptional, it must prompt a search for other causes of thyroid dysfunction.

Initial Assessment

3.4.3 Auditory assessment

Pendred syndrome is most often diagnosed during the initial assessment of a child’s hearing loss.

Hearing loss in Pendred syndrome (biallellic SLC26A4 pathogenic variations) is most often a severe and bilateral hearing loss. It can be asymmetrical. In unilateral cases, it is necessary to be very vigilant when monitoring the normal ear, which can degrade secondarily and sometimes suddenly. The severity of hearing loss varies from one patient to another. Hearing loss occurs at birth or in the prelingual period in two thirds of cases but may occur later. In these cases, the circumstances of discovery are rather related to an episode of sudden deafness or to the discovery of a goitre with hearing loss without prior etiological diagnosis. Hearing impairment may have a mixed component (related to a 3rd window phenomenon of the inner ear).

All patients require an age-appropriate auditory assessment including:

- tonal audiometry (air and bone conduction thresholds with contralateral masking);
- speech audiometry;
- tympanometry;
- ABR or ASSR for diagnosis when the child is very young or to confirm the hearing loss or to exclude aggravation if necessary.

In children under two years of age, it is recommended that objective audiometric testing is re-aligned with age-appropriate behavioral audiometric tests. These tests must be completed by objective hearing tests to determine and confirm the level of hearing impairment (OAE, ABR and ASSR).

In order to assess the impact of the hearing loss in the child, it is recommended to assess speech-and language development

3.4.4 Vestibular tests

Available studies dealing with vestibular disorders related to biallellic SLC26A4 pathogenic variations do not differentiate syndromic forms (Pendred syndrome) from non-syndromic forms (DFNB4), in part due to the low number of patients studied.
One to three quarters of patients with to biallellic SLC26A4 pathogenic variations have clinical signs of vestibular dysfunction (dizziness or instability). However, vestibular dysfunction (mainly hyporeflexia during caloric testing) appears to be present in a majority of patients even not symptomatic. There is no description of the otolithic dysfunction in Pendred syndrome today.
Thus, all patients should have a vestibular checkup that includes:

- a detailed history for vestibular symptoms;
- a VHIT;
- caloric testing to assess the function of the posterior semicircular canal
- otolithic evoced potentials (cVEMP and oVEMP).

An increase in amplitudes and a lower cVEMP threshold (to 250 and 500 Hz) has been reported in several studies in patients with LEDS (all causes combined including patients with Pendred syndrome), probably due (such as mixed deafness) to the presence of a third window.
In children with psychomotor retardation and/or important vestibular impairment, a psychomotor assessment is recommended.

3.4.5 Radiological assessment of the ear

Imaging is an integral part of the assessment of the child’s congenital hearing loss. This includes, depending on the type of hearing loss computerized tomography (CT) of the temporal bones or magnetic resonance imaging of the internal inner ear canals, or even the combination of both in an assessment for a cochlear implantation. It must be performed in a specialised centre with expertise in imaging for ENT and pediatrics.

For computerized tomography, irradiation doses must be adapted to the age of the child. Depending on the age of the child, a sedation (or general anesthesia) may be necessary.

A CT is used to analyse the middle ear and bony labyrinth

A MRI allows to visualise the membranous labyrinth. The MRI is also used to analyse cochleovestibular and facial nerves, and to search for congenital or acquired brain abnormalities.

Radiological abnormalities of Pendred syndrome are not specific to Pendred syndrome. They may be present outside this syndrome, or in children with DFNB4 (isolated hearing loss due to biallellic SLC26A4 pathogenic variations). But in case of Pendred syndrome, these anomalies are always the same:

- Bilateral expansion of the vestibule aqueduct (CT) or endolymphatic duct and sac (MRI);
- Normal cochlea or incomplete partition type II (classification of Sennaroglu : No differentiation of the intermediate and apical turns of the cochlea, with no visibility of the spiral ligament at this leve)l;
- Normal or hypoplastic cochlea;
- Normal or enlarged vestibule.

These anomalies are always bilateral, but may be more or less marked and asymetric

3.4.6 Endocrine review

- **Clinical examination**

<u>At the paediatric age</u>

- Assess weight, size, head circumference, body mass index (BMI) according to age and sex , pubertal stage and analysis of staturo-ponderal growth;
- Arterial Blood pressure;
- Palpation of the thyroid gland to search for a goitre, thyroid nodules or cervical adenopathies;
- Measurement of neck circumference
- Search for the examination of functional signs of hypothyroidism: digestive (constipation, weight gain), fatigue, drowsiness, attention deficits and learning problems, chilliness, sleep disorders.

In adulthood

- Clinical examination: age, weight, height, body mass index (BMI), blood pressure;
- Palpation of the thyroid gland and search for a goitre, thyroid nodules or adenopathy;
- Looking for functional signs of hypothyroidism;
- Looking for signs of compression due to thyroid enlargement dyspnea, dysphagia, dysphonia, vena cava superior syndrome

- **Paraclinical examinations**

Paraclinical examinations are adapted to the patient’s age at the time of diagnosis and consist mainly of:

- Measuring thyroid hormones (TSH, FT4) and testing for autoimmunity markers (anti-thyroperoxidase antibodies);
- Thyroid ultrasound by a specialised radiologist with description of the position of the thyroid, measurement of the size of the two lobes and thyroid isthmus, vascularization and echogenicity-, search for a nodular pathology with classification according to the EU- TIRADS score;
- Thyroid scintigraphy with iodine 123 perchlorate discharge test, to evaluate the uptake of iodine (Annexes 7 and 8).

3.6 Assessment of severity/extension of disease/comorbidity research/prognostic evaluation

3.6.1 Prognosis

The impact of this syndrome is primarily auditory, since the severity and early presentation of hearing loss will affect language learning and social, academic and cognitive development. Severe or profound bilateral hearing loss should prompt a discussion of cochlear implant surgery and long-term multidisciplinary follow-up.

In cases of mild to moderate hearing loss, the evolution of hearing impairment is most often marked by episodes of worsening. Hearing evolution can be progressive over several years (even during adulthood) or be accompanied by episodes of sudden deafness, tinnitus and vestibular symptoms. In the event of asymmetrical or unilateral hearing loss, special attention should be paid to the risk of progressive hearing loss in the better hearing ear. The patient should be informed about of the risk of sudden worsening of hearing. These aggravations can be triggered by mechanical trauma (even with minor cranial trauma),

sudden changes in environmental pressure, noise trauma, or in the context of upper airway infection or fever and at any age.

3.6.2 Severity

The type of the *SLC26A4* variation does not predict the evolution of the pathology (no genotype-phenotype correlation). It is estimated that 10 % of children with SLC26A4 biallelic mutations will develop Pendred syndrome. To date, there are no factors to predict the onset of this syndrome in children with hearing loss due to biallelic *SLC26A4* variations.

Neither the evolution nor the initial severity of hearing impairment have been associated with radiological abnormalities (e.g. no correlation with the size of the LEDS).

The malformation of the inner ear found in Pendred syndrome can lead to difficulties during cochlear implant surgery:

- Risk of leakage of peri-lymphatic fluid (Gusher) which is in practice should be anticipated and controlled for during surgery;
- Risk of malposition of the electrode holder and partial insertion of the electrode holder in case of Gusher;
- More difficult clogging of the cochleostomy;
- Increased risk of vestibular damage or post-operative dizziness.

There is an increased risk of bactorial meningitis when there is a malformation of the inner ear. Therefore, pneumococcal vaccination is recommended in patients with Pendred syndrome. It is based on the 13-valent vaccine (Prevenar) and combines the 13-valent (Prevenar) vaccine with the 23-valent vaccine (Pneumovax) from the age of 6 years (Please refer to your own national guidelines for pneumococcal vaccination in high risk patients).

3.7 Discussion of the diagnosis with the patient and it's parents/caregivers

The announcement must be organised in a specialised centre, or in a centre with professionals in collaboration with a specialised centre (Annex 2). The presence of a psychologist is recommended.

The main characteristics of the syndrome, the possibilities of care and follow-up are explained to parents and the patient according to their age at the time of the diagnosis. Also discussed are the mode of transmission and genetic counselling (see next chapter).

The possibility to become a member of a patient association is discussed.

Psychological care for the child and his or her family may be offered.

It is desirable that a document containing the above-mentioned elements be given to the parents and the patient according to their age. A copy is provided to the pediatrician or family doctor.

3.8 Genetic counselling

Pendred syndrome (and isolated deafness DFNB4) are transmitted with an autosomal recessive mode. A couple of parents who have a child with Pendred syndrome have a 1/4 risk of having one affected child in every pregnancy, be it a boy or a girl (Appendix 3).

An affected adult has a very low risk of having affected children except in the case of a union with a person with the same pathology or in case of consanguinity.
Similarly, the frequency of *SLC26A4* heterozygous pathogenic variation in the general population is low (<1 %), the risk of recurrence of the syndrome is low for a healthy relative, accepted in case of consanguinity. However, genetic counselling may be offered to the patient’s spouse or other family members.
If there is a risk of recurrence during pregnancy, the couple may request a prenatal diagnosis or a preimplantation diagnosis from a multidisciplinary Centre for Pre-natal Diagnostics. The latter assesses the eligibility according to the terms of the law prevailing in the country of interest, and the feasibility of this request.
For all these steps, it is recommended to meet with clinical geneticists familiar with this condition.

4 Therapeutic Management

4.1 Objectives

The main objective of ENT support is optimal hearing rehabilitation by uni- or bilateral hearing aids depending on the severity of the hearing loss. In cases of severe to profound bilateral congenital hearing loss, early cochlear implantation should be proposed. In mild to moderate hearing loss or late onset hearing loss, the management will also aim to preserve the hearing by limiting hearing fluctuations and by taking urgent care of episodes of sudden deafness.
The management of possible vestibular symptoms is one of the objectives of care.

On the thyroid side, management consists of detecting and correcting hypothyroidism when it appears:

- Detect and explore goitre and thyroid nodular pathology;
- Optimise growth;
- Educate the patient to ensure compliance and therapeutic follow-up;
- To point out the potential complications of hypothyroidism and its substitution, as well as the complications of goitre;
- Improve the quality of life in the paediatric and adult ages.

4.2 Professionals involved (and coordination arrangements)

The professionals involved are identical to those involved in the initial review.

4.3 Therapeutic management (pharmacological and other)

There is no specific treatment for Pendred’s syndrome, but there is a management of the symptoms associated with this pathology.

4.3.1 ENT support

4.3.1.1 Hearing rehabilitation

Hearing rehabilitation consists in the use of hearing aids or cochlear implantation. A conventional hearing aid is indicated for mild to moderate hearing loss. In cases where conventional hearing aids are insufficient, a cochlear implantation may be considered and should be performed with the local eligibility criteria (criteria for reimbursement may be different between countries).

4.3.1.1.1 Conventional hearing aid

The purpose of the conventional hearing aid is to restore bilateral hearing. Hearing aids can be worn uni- or bilateral depending on whether the hearing loss is one-sided or bilateral. Hearing aids are recommended for children with permanent bilateral hearing loss with an average hearing threshold of more than 40 dB. Children with uni or bilateral mild hearing loss are also offered hearing aids depending on the impact on speech-language acquisition and functioning in daily life. It is important to use audio-prosthetists specialised in the care of severe hearing loss and/or the child. Audio-prosthetic support includes the choice and adaptation of prostheses, control of their efficacy, follow-up, and prosthetic education. Patients should be encouraged to be regular users similar as for any hearing loss regardless of etiology.

4.3.1.1.2 Cochlear implantation

Cochlear implantation is indicated in case of bilateral severe to profound hearing loss and allows for very good hearing performance:

- In case of bilateral severe to profound hearing loss;
- In the event of hearing loss in a child or adult, when speech discrimination is insufficient despite well-adjusted hearing aids to achieve adequate speech development (criteria may differ between countries);
- In case of fluctuating hearing loss and a major impact on the speech-and language development.

The indication of cochlear implantation is carried out after a multidisciplinary assessment (clinical, subjective and objective audiometric, vestibular, radiological, speech-language, psychological) in a specialised centre.
Implantation may be unilateral or bilateral, simultaneous or sequential depending on the hearing, vestibular deficit and age of the patient (before or after the acquisition of walking in the child). In case of unilateral implantation, it is important to encourage the use of the contralateral hearing aid. A contralateral implantation (sequential bilateral) is proposed in the event of progressive hearing loss occurring at any time after the first implant.

The pre-and peroperative management should be discussed with the anesthesiologist, ENT surgeon and endocrinologist (in cases of thyroid dysfunction). Precautions should be put in place to is to reduce the specific risks associated with the malformation of the inner ear.

Prevention of hearing fluctuations

Due to the risk of sudden worsening of the hearing:

- It is recommended to avoid sports at risk of head trauma (contact sports) and practices at risk of barotrauma (diving, use of a parachute, playing wind instruments, carrying heavy loads, Valsalva maneuvers).
- It is advisable to be attentive to the possibility of hearing loss in case of fever or upper airway infections, which must prompt an urgent appointment in the ENT department to obtain an audiogram.

4.3.1.3 Support for hearing fluctuations

Support for sudden uni or bilateral hearing loss is considered a medical emergency. It is based on corticosteroid treatment initiateds immediately after the confirmation of a sudden hearing loss. This is not

specific to patients with biallellic pathogenic variations of *SLC26A4.* Treatment of sudden hearing loss is considered a medical emergency and should be performed according to local guidelines of the institution.

Speech-language rehabilitation

Speech-language rehabilitation is an important part of care at each stage:

- In a child who has a pre-lingual deafness: Start speech-language rehabilitation from the start of the hearing rehabilitation. The objectives are the development of oral language: hearing education in the sound world in a playful way, to develop the capacity of the child of expressing himself in his mother language during activities of daily life.
- The number of weekly sessions is determined by the speech therapist based on the initial assessment. In case of a post lingual progressive hearing loss rehabilitation will aim at: development of lip reading to facilitate multimodal speech integration, strengthen cognitive and executive skills involved in the processing of verbal information.
- In the case of cochlear implantation, speech-language education should be continued after implant activation in order to achieve a gradual improvement in patients’ intelligibility.

4.3.1.4 Management of Balance Disorders

The management of vestibular symptoms is not specific to patients with Pendred syndrome. It is mainly based on:

- Symptomatic medical treatment combining anti-vertiginous and anti-emetic (metoclopramide, used with caution and second intention in children after 1 year of age) in the event of an acute dizziness attacks and in the absence of contraindications;
- Vestibular rehabilitation (in adults or older children) has its full place in the case of chronic vertiginous symptoms;
- Treatment by a psychomotrician in case of psychomotor delay in the young child.

4.3.2 Endocrine Support

4.3.2.1 Treatment of hypothyroidism

4.3.2.1.1 Hypothyroidism proven

Hypothyroidism is defined by a rise in TSH concentration associated with a decrease in serum FT4 concentration. The treatment of hypothyroidism is based on oral L- thyroxine upon confirmation of the diagnosis. The target concentration of TSH should be adapted to age and presence of comorbidities. The table below provides initial dosages.

Congenital hypothyroidism	Hypothyroidism of the child	Adult hypothyroidism
15 µg/kg/d	1-3 µg/kg/d	1.6-1.8µg/kg/d

There is no evidence for the use of liothyronin (T3L) or L-thyroxine/liothyronine combination.

4.3.2.1.2 Subclinical hypothyroidism

Subclinical hypothyroidism is defined by an increase in TSH concentration associated with a normal FT4 concentration. The interest in substituting subclinical hypothyroidism in patients with Pendred syndrome has not been evaluated.
In children: treatment with L-thyroxine if TSH >10mUI/L or in the presence of a goitre to prevent the growth induced by increased levels of TSH
In adults: proposed treatment with L-thyroxine in TSH >10mUI/L associated with thyroid autoimmunity (AC-anti-TPO presence) and/or the presence of a symptomatology compatible with hypothyroidism or in the presence of a goitre to prevent the growth of TSH elevation.

The target concentration of TSH should be adapted to age and to comorbidities.

4.3.2.2 Management of goitre and nodular pathology

4.3.2.2.1 Monitoring

In the absence of compressive signs and nodular pathology, clinical and ultrasound monitoring of goitre can be proposed. At the pediatric age a thyroid ultrasound is proposed once a year and is adult once every 2 years.

4.3.2.2.2 Thyroid surgery

Thyroidectomy should be avoided as far as possible, especially in children in order to limit the risk of post-operative complications. Its indication and implementation are the responsibility of expert centres after multi-disciplinary consultation. Thyroidectomy may be legitimate in case of diving or compressive goitre (with dyspnea, dysphagia, dysphonia or vena cava superior syndrome). In these cases, a total thyroidectomy is recommended.
A thyroidectomy (total or partial) may also be proposed in case of suspicious nodular pathology identified by the recommended explorations (thyroid ultrasound and cytology).

4.3.2.2.3 Other treatments

Iodine iodine therapy 131 a.m. intended for volume reduction of the goitre has not been evaluated in Pendred syndrome.

The treatment with L-thyroxine to reduce goitre has not been evaluated in Pendred syndrome. These two treatments are therefore at present not recommended in Pendred syndrome.

4.4 Therapeutic education and lifestyle modification (on a case-by-case basis)

Therapeutic education will be adapted on a case-by-case basis depending on the severity of the hearing loss:

- In case of mild to moderate bilateral hearing loss or or unilatal hearing loss, the therapeutic education must emphasize the risk of worsening and the need for prompt management of hearing deterioration. Similarly, situations associated with a risk of sudden deafness should be avoided (sports at risk of head injury, practices at risk of barotrauma);
- In case of severe to profound hearing loss requiring cochlear implantation, therapeutic education is in line with that of all patients with cochlear implant and insists on the need for equipment maintenance, permanent use, speech rehabilitation, and prolonged follow-up;
- Information and prevention of meningitis.

Therapeutic education is repeated during initial diagnosis as part of congenital hypothyroidism.

4.5 Contra-indicated treatments

In the management of hearing impairment, surgery of the endolymphatic sac is not recommended due to a risk of worsening post-operative hearing.

4.6 Link to patient associations to be adapted depending on the local situation

Currently, there is no patient association specifically dedicated to Pendred syndrome.

Relevant support and advocacy are mainly provided by associations for people with hearing loss and those with cochlear implants.

For thyroid-related issues, both healthcare professionals and patients are encouraged to reach out to local patient associations specializing in thyroid disorders.

5 Follow-up

5.1 Objectives

Due to the evolutionary nature, the audiological assessment should be repeated at least annually if the hearing loss is stable, or more often depending on the patient’s symptoms.

The objectives of patient follow-up are:

- Monitoring of hearing evolution and taking care of any deterioration. Special attention should be paid to the contralateral ear in case of initial unilateral hearing loss;
- Regular monitoring of hearing aids and/or cochlear implantation;
- Monitoring of audio-prothesthetic benefit and/or cochlear implant;
- Screening for other otological pathologies that may worsen the hearing loss(chronic sero-mucosa otitis, repeated acute otitis, other chronic otitis);
- Screening for potential difficulties in school, social or professional issues;
- Screening for possible psychological disorders related to hearing impairment;
- Screening for a goitre or thyroid nodular pathology;
- Adaptation of treatment with L-thyroxine: effectiveness, tolerance and compliance;
- Ensure a child/adult transition.

5.2 Professionals involved (and coordination arrangements)

The professionals involved in the follow-up are identical to those involved in the initial review and takeover.

5.3 Timing and content of consultations

5.3.1 For hearing loss:

Regular follow-up by the ENT is necessary and the timing of consultations is to adapt to each patient’s hearing and vestibular symptoms.
In children under 6 years of age, bi-annual follow-up is recommended. In adults and children over 6 years of age, at least annual consultation is required.
During the follow-up consultation, the ENT surgeon will evaluate :

- The presence of hearing fluctuations experienced by the patient;

- The presence of dizziness and/or instability;
- Micro-otoscopy;
- Obtain an audiogram, with a technique adapted to the age of the patient with and without hearing aids to be compared to previous audiograms.

5.3.2 For endocrinological monitoring

At the paediatric age:

If hypothyroidism is diagnosed in the neonatal period (exceptional in Pendred syndrome): an initial check of thyroid balance is indicated 2 weeks after starting treatment and every 2 weeks until normalization of TSH, then every 1-3 months until 1 year of age, every 2-4 months between 1 and 3 years and every 6 months until the end of growth.

If diagnosis is made at paediatric age: a thyroid balance is proposed 4 weeks after starting treatment as well as after each modification of the treatment. The rate of monitoring of the thyroid balance depends on the age of the child as described above.

In adulthood:

Consultation at 6 months and every 12 to 24 months. Monitoring of TSH at 6 and 12 weeks after introduction of L-thyroxine or after each dose change and then monitoring of annual TSH.

Patient follow-up is done in consultation.

- **Each visit:**
  - Clinical examination: weight, height, body mass index (BMI), cranial perimeter before 4 years and construction of growth curves until the end of growth;
  - Blood pressure;
  - Palpation of the thyroid gland and search for a goitre, thyroid nodules or adenopathy;
  - Looking for functional signs of hypothyroidism;
  - Looking for signs of compressive goitre: dyspnea, dysphagia, dysphonia, vena cave superior syndrome;
  - Check for treatment compliance;
  - Assessment of lifestyle, education and professional activity;
  - Evaluation of the blood thyroid balance and adaptation of treatment if necessary;

- Ultrasound monitoring in case of goitre or thyroid nodule. In case of nodular pathology, surveillance is based on current recommendations without specificity related to Pendred syndrome.

5.4 Child-adult transition

For Pendred syndrome, the transition from the care of the patient from pediatrics to adult medicine is important to ensure optimal continuity of care for the patient. This involves the collaboration of care teams to prevent the loss of follow-up and/or complications of the disease that may occur in adulthood. The age of transition will be adapted according to each patient but may be between 16 and 19 years of age. The evolutionary nature of the disease and the specificity of management (especially in the case of cochlear implants) make this fundamental step. The patient must be accompanied, and the transmission of medical information must be made between specialists with the preparation of detailed reports.
It is important to renew with the patient when young adults the initial information given to their parents about the evolution of their pathology, the need for long-term follow-up and genetic counselling.

The first adult consultation:

- **ENT**
  - Repeat the history of hearing loss (transmission of audiometric and electrophysiological reports and examinations);
  - Repeat the otological clinical examination;
  - Make an initial audiometric check in the adult service;
  - Underline the importance of regular follow-up and explanation of situations that should lead to urgent consultation;
  - Inform the patient about unwanted behaviour with increased risk for hearing loss;
  - Inform the patient about social and school approaches (university adaptations);
  - Assess the level of understanding of his/her pathology by the young adult;
  - Transmit radiological data to avoid duplication of examinations.
- **Endocrinology**
  - Repeat the history of thyroid disorders of Pendred syndrome (goitre, thyroid nodular pathology and hypothyroidism);
  - Assess the level of understanding of thyroid disease;
  - Stress the importance of compliance and thyroid monitoring;
  - Perform a somatic clinical examination including the thyroid.

- **Genetics**

  - Reexplain the mode of transmission of Pendred syndrome;
  - Assess the risk of recurrence during pregnancy;
  - Support any request for prenatal or pre-implantation diagnosis.

5.5 Special Case of Pregnancy

There is no thyroid contraindication to begin pregnancy as part of Pendred syndrome. However, in case of preconception hypothyroidism, the dose of L- thyroxine should be systematically increased by 30 to 50 % from diagnosis of pregnancy to compensate for physiological increase in needs and careful monitoring with a monthly TSH dosage during the entire pregnancy will be initiated. In the absence of pre-symptomatic hypothyroidism, monthly monitoring of TSH will also be carried out. Monitoring of goitre will also be carried out in view of the risk of pregnancy-related increases.
There are currently no data showing an increased risk of worsening of hearing thresholds during pregnancy and postpartum

Annex 1. List of participants

- This work was coordinated by Dr. Sandrine Marlin, coordinator of the reference centre for genetic deafness (Institut Imagine — APHP Necker Enfants Malades).

Participated in the development of the PNDS:

Editors

- Dr Sandrine Marlin, clinical geneticist, Paris
- Dr. Athanasia Stoupa, Pediatric Endocrinologist, Paris
- Dr Frédéric Illouz, endocrinologist, Angers
- Dr Ghislene Lahlou, ORL Adults, Paris
- Dr. François Simon, ORL Paediatric, Paris
- PR Natalie Loundon, ORL paediatric, Paris
- Dr. Laurence Jonard, molecular biologist, Paris
- Dr. Monique El Malleh, Radiologist, Paris
- Dr Charlotte Hautefort, ORL, Paris
- PR Sebastien Gaujoux, digestive surgeon, Paris
- Dr Claire Bournau-Salinas, nuclear radiologist, Paris

Multidisciplinary Working Group

- PR Sylvie Odent, medical geneticist, Rennes
- Dr Isabelle Olivier-Petit, endocrinologist, Toulouse
- Dr Miriam Ladsous, endocrinologist, Valencian
- PR Vincent Couloigner, ENT, Paris
- Dr Sophie Tronche, ORL, Paris
- PR Dominique Chevalier, ENT, Lille
- Dr Anne Francoise Roux, medical geneticist, Montpellier
- Dr. Jean Michel Klein, ORL, Paris
- Dr. Elisabeth Plet, Endocrinologist, Malesherbes

Rereaders

- Dr Margaux Serey-Gaut, medical geneticist, Paris
- Afida Djabri, Research Officer, Paris

- An Boudewyns, ENT, Antwerp Belgium

Declarations of interest

All participants in the development of the NDP completed a declaration of interest. Declarations of interest are available online and can be found on the website of the reference centre(s).

Annex 2. Contact Details of Centers of Expertise and Competence

Patients with Pendred syndrome may require multidisciplinary care across various specialties, including audiology, endocrinology, and clinical genetics. For access to expert centres across Europe, we refer to the networks of the European Reference Networks (ERNs), which bring together centres of expertise for rare and complex diseases.

Although this protocol does not provide an exhaustive list of reference or competence centres, up-to-date information on participating centres and contact details can be found via the official websites of the relevant ERNs:

- **ERN CRANIO (for craniofacial anomalies and hearing loss):** https://ern-cranio.eu/
- **ENDO-ERN (for rare endocrine conditions, including thyroid disorders):** https://endo-ern.eu/

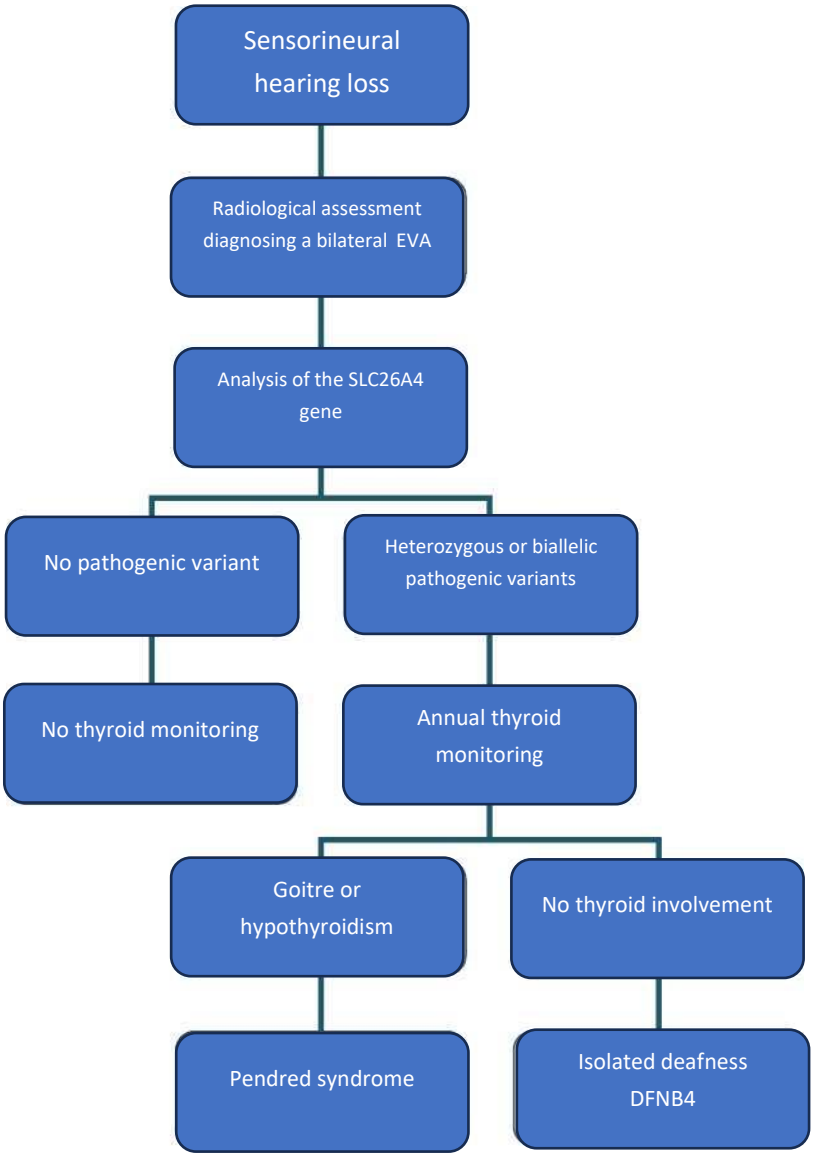
These websites include directories of affiliated healthcare providers and patient representatives, allowing patients and professionals to identify appropriate centres within their country or region.

- Patient Association

As of today, there is no patient association specifically dedicated to Pendred syndrome.
Patients and professionals may instead refer to broader organizations, such as associations for people with hearing loss, associations of cochlear implant users, and associations for individuals with thyroid disorders.

Relevant networks include the Endocrine and Craniofacial European Reference Networks (ENDO-ERN and ERN CRANIO). Further information and a list of patient representatives can be found on the ERN CRANIO website (https://www.ern-cranio.eu/patient-organisations) and the ENDO-ERN website (https://endo-ern.eu/patients/endo-ern-patient-representatives/).

Annex 3. Decision tree for diagnosis



Annex 4. Autosomal recessive transmission

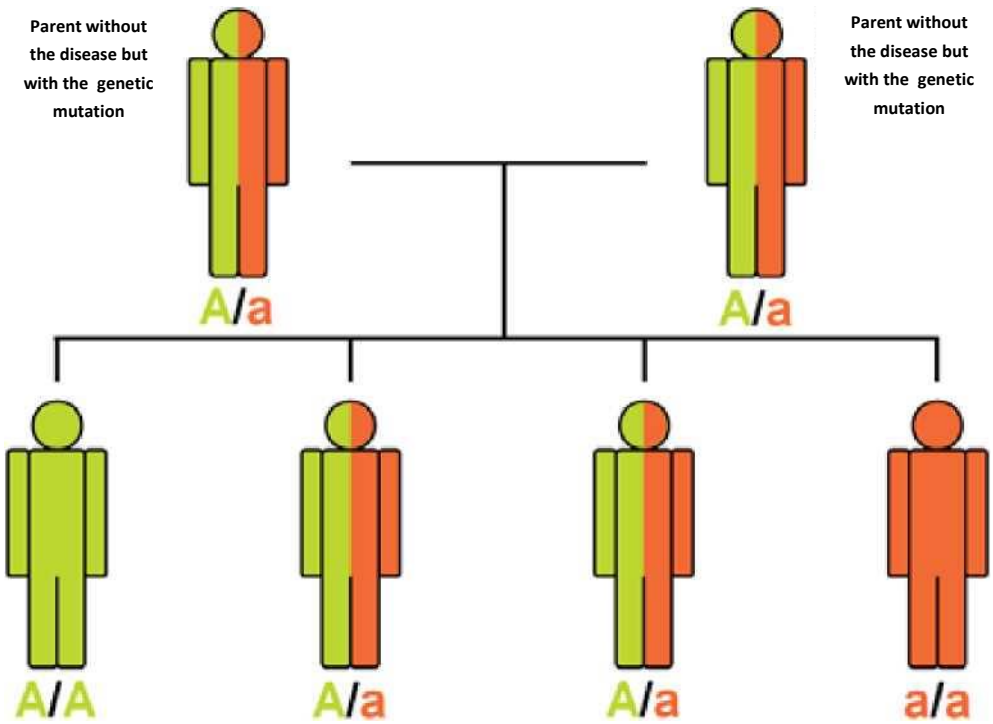
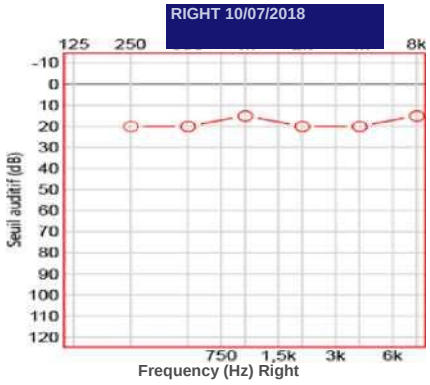
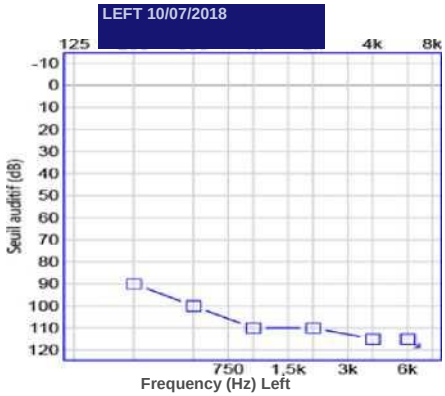
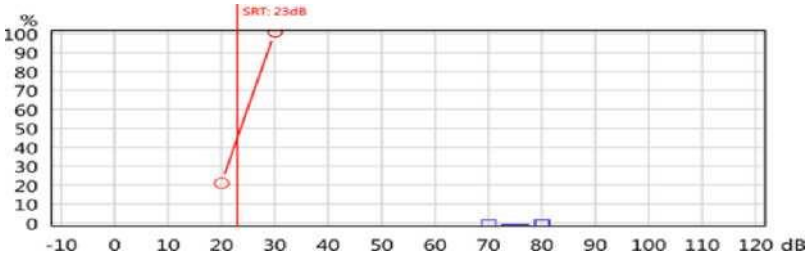


Figure 1: *Illustration of autosomal recessive transmission.*
Both parents carry the mutated gene (a) and the normal gene (A), but they are not ill (it is said that they are heterozygous healthy carriers). The child (a/a) inherited the two mutated genes from his father and mother: he has Pendred syndrome (he is said to be sick homozygote). Like their parents, children (A/a) are not ill but carry the mutated gene and may transmit it to their offspring. They are “healthy carrier heterozygous”. The child (A/A) did not inherit any mutated genes, neither that of his mother nor that of his father: he is not ill and is not at risk of transmitting the disease. They say he’s a healthy homozygote. © Orphanet

Annex 5. Examples of audiograms







Legend

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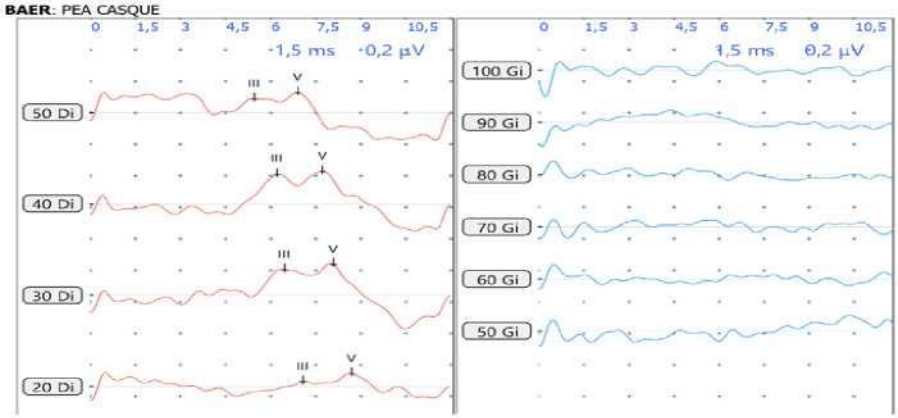


***Figure 2**: Audiometry and ABR characteristics of a deep deafness of left perception (in blue). The right hearing is normal (red).*

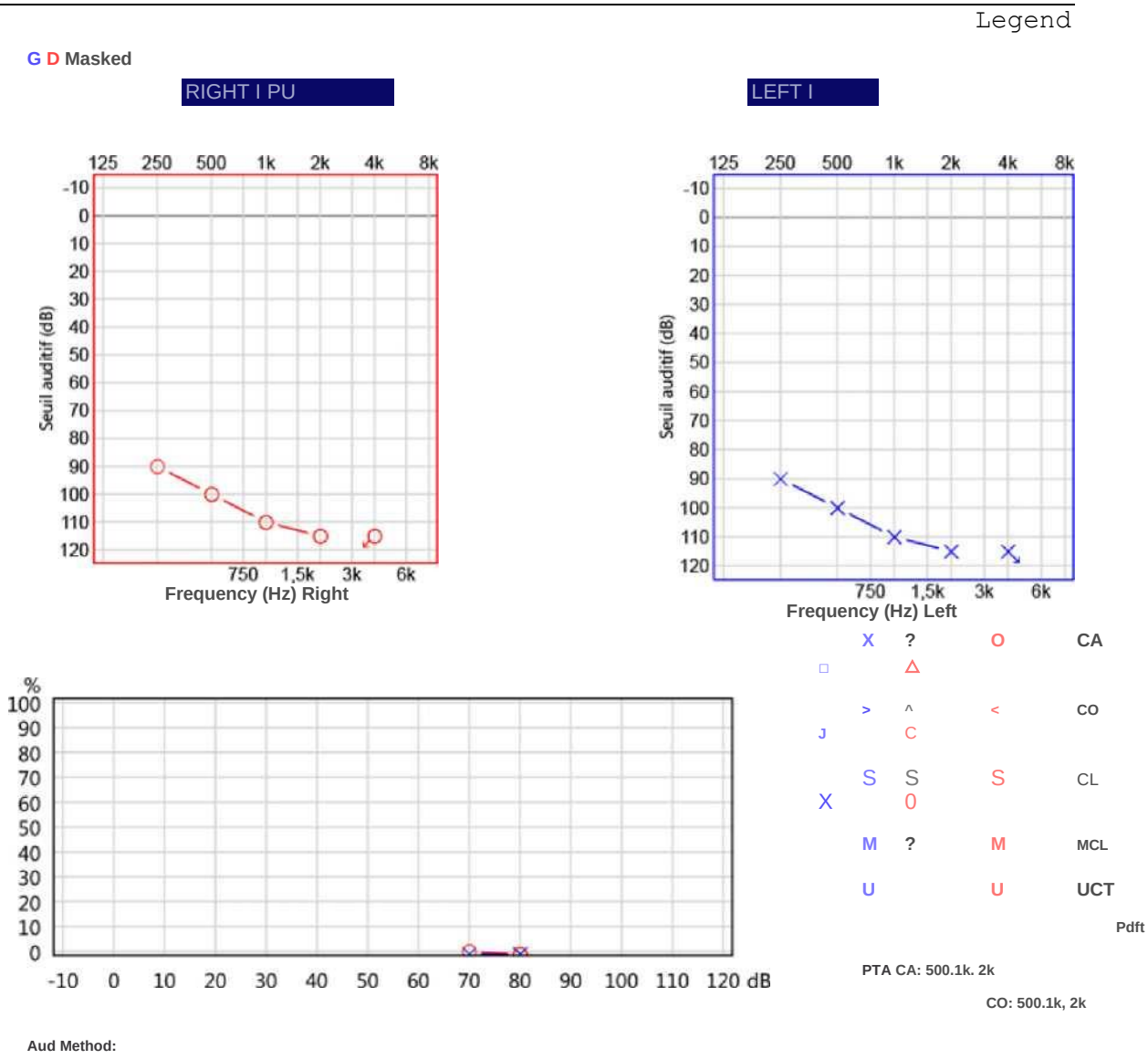


Figure 3: *Audiometry and ABR characteristics of a deep bilateral perception deafness with brutal worsening of the hearing on the right (red). In this case, the indication of emergency cochlear implantation should be discussed in the absence of recovery after a few weeks.*

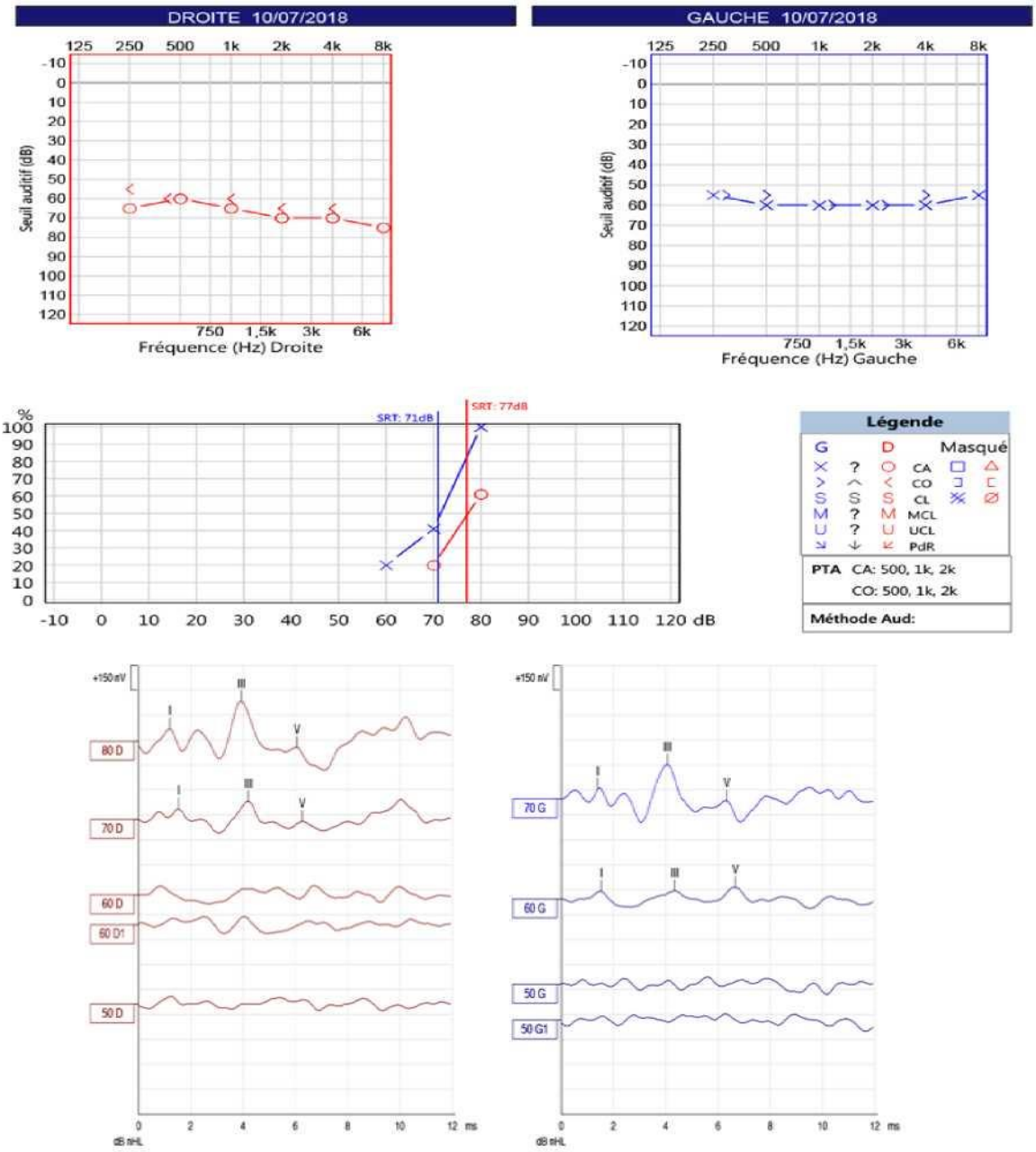


Figure 4: *Audiometry and PEA characteristics of a medium bilateral perception deafness with apparatus.*

Annex 6. Imagery

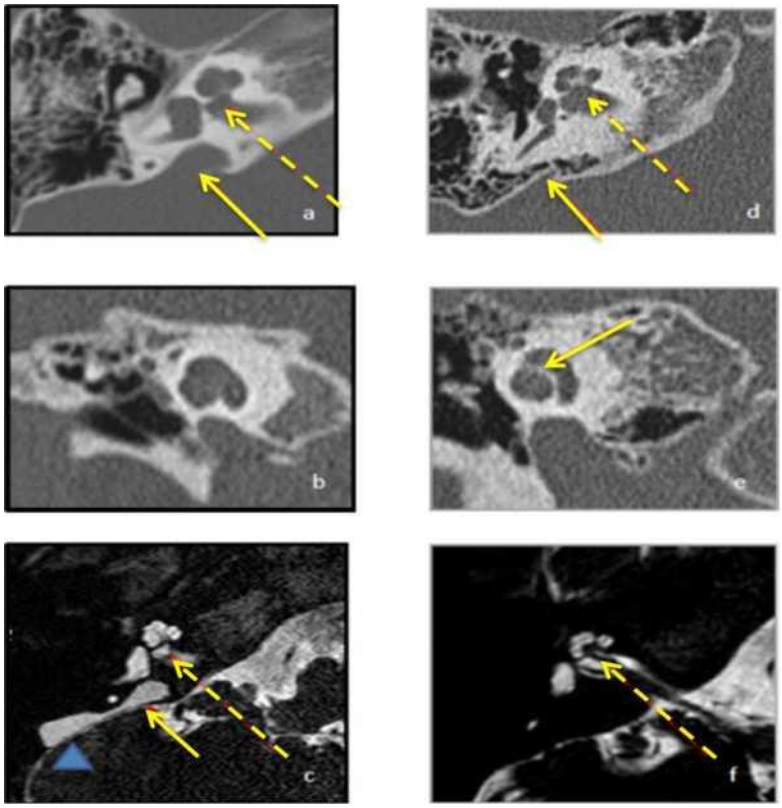


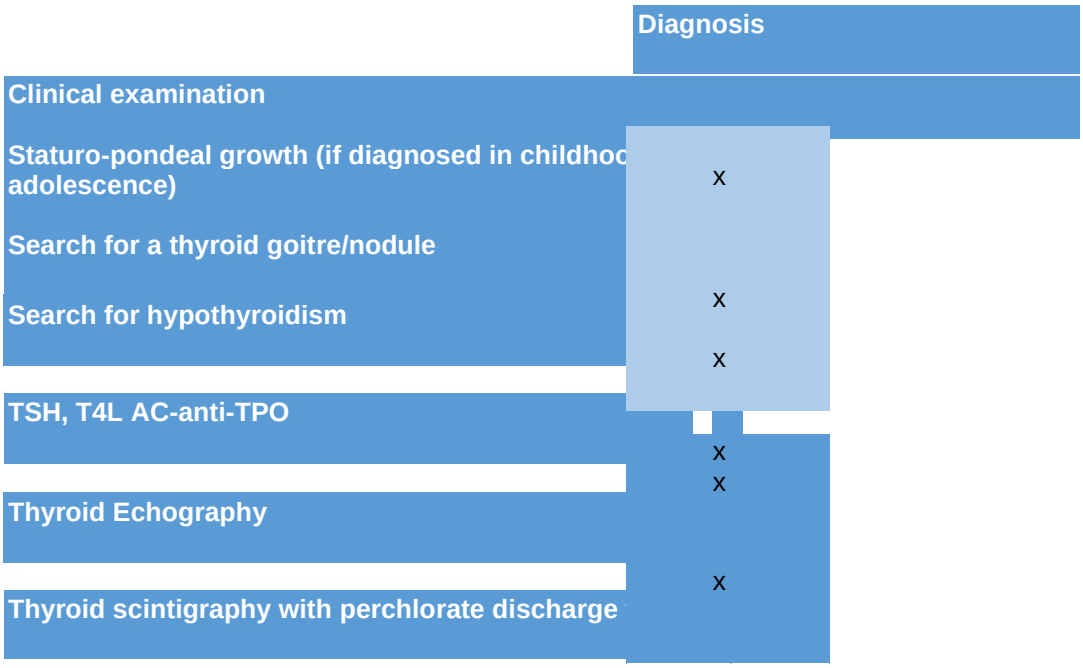
***Figure 5**: Labyrinthic malformations of a Pendred syndrome identified with the temporal bones CT and the MRI of internal auditory ducts.*

***Images a, b, c**: right ear of a patient with Pendred syndrome.*

***Images d, e, f**: normal right ear.*

- ***Images a, d**: axial cutting CT: **a**: modiolus hypoplasia (dotted arrow), enlarged vestibule aqueduct (arrow).*
- ***Images b, e**: front cutting CT: **B**: there is no spiral blade between the intermediate tower and the apical tower of the cochlea (arrow).*
- ***Images c, f:** MRI, high resolution 3D T2 sequence, axial cut: **C**: absence of spiral blade between the upper towers of the cochlea, hypoplasia of the modiolus (dotted arrow), dilation of the endolymphatic sac (arrow), including in its extra-osseous part (arrow head).*

Annex 7. Endocrinological management when diagnosed with Pendred syndrome



* Thyroid scintigraphy coupled with the perchlorate discharge test may be proposed for any suspicion of Pendred syndrome. However, it is not mandatory in typical cases, thanks to molecular diagnosis. In the case of *SLC26A4* bilallelic pathogenic variations, this test could be predictive of the development of hypothyroidism or goitre.

Endocrinological monitoring of Pendred syndrome

	0-3 years*	3 to 16 years	Pediatric/Adult Transition	Adult >18years
Clinical examination				
Growth staturo-weight	1/3 months	1/6 months		
Search for a thyroid goitre/nodule	1/3 months	1/6 months	x	1/1-2 years
Search for hypothyroidism	1/3 months	1/6 months	x	1/1-2 years
TSH, T4L	1/3 months	1/6 months	x	1/1-2 years
Thyroid Echography	1/year	1/year	x	1/3 years

* If diagnosis during the neonatal period (congenital hypothyroidism), follow-up should be based on the international consensus for the management of congenital hypothyroidism.

The usual pediatric follow-up of the patient with mandatory examinations should be continued during the first 6 years.

Annex 8. Scintigraphy and potassium or sodium perchlorate test

Thyroid scintigraphy with the potassium or sodium perchlorate discharge test will evaluate the lack of iodine organisation, which is characteristic of Pendred syndrome. However, a so-called ‘normal’ perchlorate test does not exclude Pendred syndrome. This test may therefore be useful but is not indispensable in particular since the possibility of a genetic diagnosis (see 3.5.4). However, it has been shown that in the case of *SLC26A4* bilallelic pathogenic variations, the presence of a load test >30 % may be predictive to the onset of hypothyroidism or goitre. The first step in this test is the realization of a thyroid scintigraphy with iodine 123, which shows the percentage of basal fixation of the thyroid gland. The second step is the measurement of the growth of thyroid fixation following administration of potassium perchlorate or sodium. There are a number of ways in which this test can be re-enacted and interpreted. At 180 minutes of iodine 123 injection, the patient ingested potassium perchlorate at the dose of 1 g in adults and 15 mg/kg in children. Thyroid activity is measured at 15, 30, 45 and 60 minutes after taking perchlorate (other authors propose durations up to 2 hours). The percentage change in fixations before and after ingestion of perchlorate is then calculated. The result is therefore given as a change in the percentage of the initial rate. The discharge test is said to be negative, i.e. there is no failure to organise iodine, if this percentage is < 10 %. The value >10 % is sometimes used to speak of a positive test, i.e. it exits a disorder in the organisation of the iodides, as is most often the case with Pendred syndrome. Note that higher values are sometimes retained (up to 30 %).

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Recommendations

1. Formal consensus of experts on the Audiome of Adult and Childhood — 2016 — French Society of ORL
2. Guide to Good Practice of the Voice Audiome — 2009 — French Audiology Society
3. Guide to Radiological Procedures: Quality and Optimisation of Doses (updated on 26/03/2014 by the French Radiology Society (SFR))
4. Guide to the Use of Medical Imaging Examinations: gbu.radiologie.fr (updated on 03/04/2013 by SFR)
5. Practical Guide to Diagnostic Imaging for Radiological Physicians (updated on 07/03/2013 by the SFR)
6. Indications of cochlear implant in adults and children — 2018 — ORL French Society
7. Deafness of the child: family support and follow-up of the child from 0 to 6 years — 2009 — HAS