CASE REPORT

Delayed diagnosis of Pendred syndrome

Natalie Smith,¹ Jean-Marie U-King-Im,² Janaka Karalliedde³¹KCL Medical School, King's College London School of Medical Education, London, UK²King's College Hospital NHS Foundation Trust, London, UK³Guy's and Saint Thomas' NHS Foundation Trust, London, UK**Correspondence to**Natalie Smith,
natalie.n.smith@kcl.ac.uk

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SUMMARY

We describe a case of a delayed diagnosis of Pendred syndrome. The patient had a history of hearing loss from childhood and presented to the endocrine clinic when aged 32 with an enlarging goitre. The characteristic Mondini deformity was noted on auditory canal MRI scan. Genetic tests confirmed the diagnosis. Pendred syndrome is an autosomal recessive disorder, characterised by congenital sensorineural hearing loss, goitre and impaired iodide organification and can present at any age. We highlight to the general physician the classical features of this syndrome that would aid early diagnosis.

BACKGROUND

Pendred syndrome, an autosomal recessive disorder, is the most common syndromal form of hearing loss and involves abnormalities of the cochlea, varying degrees of sensorineural hearing loss and diffuse thyroid enlargement/goitre.¹ Auditory canal MRI scans can support the diagnosis by demonstrating enlarged vestibular aqueducts (Mondini deformity). In a recent study, this characteristic MRI feature was present in 49 out of 57 cases, which lead authors to suggest that the disorder be characterised by sensorineural hearing loss with enlarged vestibular aqueducts, sometimes associated with goitre.² Alternative proposed criteria are bilateral sensorineural hearing loss in combination with goitre, hypothyroidism and/or a congenital abnormality of the inner ear.³ However, thyroid function can frequently be normal in Pendred syndrome, even with significant goitre. With such variation in clinical features, genetic testing to identify pathogenic variants in the *SLC26A4* gene is increasingly used in order to confirm the diagnosis. We report a

case of Pendred syndrome that was not diagnosed until the patient presented in her thirties to an endocrine clinic with enlarging goitre. Our case report summarises the recent literature of Pendred syndrome and the diagnostic tests that would aid the prompt diagnosis of this condition.

CASE PRESENTATION

A 32-year-old woman presented to the endocrine clinic with an increased swelling in her neck over 2 years. She had a medical history of severe hearing loss since early childhood. Her main mode of communication is signing (British sign language) and lip-reading. The patient was unaware of any family history of thyroid disease, goitre or hearing loss. Her partner also has hearing loss due to an unknown cause.

On examination she had a large goitre extending retrosternally with irregular small nodules palpable, no audible bruit, negative Pemberton's sign (facial plethora when both arms are raised, caused by an enlarged thyroid compressing venous return in the thoracic inlet), no abnormal pigmentation or proximal myopathy and normal brisk deep tendon reflexes elicited in all four extremities.

INVESTIGATIONS

The most recent audiograms demonstrating bilateral profound sensorineural hearing loss with two responses in the right ear; 85 dB at 250 Hz and 100 dB at 500 Hz and three in the left; 90 dB at 250 Hz, 110 dB at 500 Hz and 120 dB at 1000 Hz, with no recordable bone conduction (figure 1).

Thyroid function tests were normal with a TSH of 2.24 mIU/L (normal range 0.27–4.2), T4 of 15.4 pmol/L (normal range 12–22), T3 of 5.5 pmol/L (3.5–7.8) and antithyroglobulin antibodies 3 U/mL

Figure 1 Audiogram demonstrating profound sensorineural hearing loss with two responses in the right ear; 85 dB at 250 Hz and 100 dB at 500 Hz and three in the left; 90 dB at 250 Hz, 110 dB at 500 Hz and 120 dB at 1000 Hz, with no recordable bone conduction.

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Figure 2 Ultrasound scan of the right thyroid lobe, showing the largest nodule, measuring 42×17×38 mm.

Figure 3 Technetium thyroid scan showing increased uptake (uptake function 23.9%) and markedly heterogeneous tracer distribution in an enlarged thyroid gland. Focal areas of increased uptake in the upper and mid regions of the right lobe.

(normal range 0–150). Thyroid autoantibodies were not raised. However, in the past she has had a low T4 (between 8 and 10 pmol/L) and thyroid-stimulating hormone (TSH) at the upper range of normal between 4 and 5 mIU/L and possible symptoms of hypothyroidism; weight gain of 3–5 kg over the last 2–3 years and tiredness.

Ultrasound scan showed an enlarged thyroid gland with multiple nodules of varying echogenicities, the largest was in the right lobe, measuring 42×17×38 mm (figure 2). Fine needle aspiration of this nodule was Thy3f, demonstrating features of a follicular lesion representing a dysrhormonogenetic goitre.

A technetium thyroid scan showed increased uptake and markedly heterogeneous tracer distribution in an enlarged thyroid gland, with more focal areas of increased uptake in the upper and mid regions of the right thyroid lobe (figure 3). The uptake function was calculated at 23.9% (normal range, 0.4–4.0%).

Figure 4 Axial T2 CISS: The Mondini malformation is demonstrated. The red arrows show marked bilateral dilation of the endolymphatic sacs, and the white arrows show dysplastic cochleas, with coalescence of the apical and middle turns. The vestibules are also mildly enlarged (arrowheads). CISS, constructive interface in steady state.

An MRI scan of the auditory canals was undertaken. This demonstrated the characteristic Mondini deformity of Pendred syndrome; marked bilateral dilation of the endolymphatic sacs (which are of a lower signal due to different protein content, a frequently seen appearance) and dysplastic cochlea, with coalescence of the apical and middle turns and mildly enlarged vestibules (figure 4).

On genetic testing, a homozygous mutation in c.991_1001+7del in CCCCA in exon 1 of the *SLC6A4* gene was found, confirming a diagnosis of Pendred syndrome. There was no history elicited of consanguinity in the family.

The results of all investigations were reviewed and discussed at a thyroid multidisciplinary meeting attended by specialists from pathology, radiology and endocrine surgery.

TREATMENT

There is no cure for Pendred syndrome. However, in view of the fine needle aspiration result and possible risk of malignancy being described in some cases of Pendred syndrome, thought to be around 1%,^{4–9} as well as the large retrosternal goitre, which may cause physical obstructive symptoms in the future, the conclusion of the multidisciplinary team meeting was to consider total thyroidectomy as the best option. British Thyroid Association recommends consideration for thyroidectomy for Thy3f lesions by the multidisciplinary team if additional indications are present.¹⁰ This was discussed in detail with the patient aided by a British sign language interpreter and the patient consented for the procedure.

Total thyroidectomy was performed for the goitre. The thyroid gland weighed 267.5 g and measured 120×100×20 mm. The right lobe contained colloid-filled cysts, in keeping with a multinodular goitre, and the left lobe contained multiple macroscopic and microscopic adenomatoid nodules, comprised follicular cells arranged in a microfollicular pattern. There was no evidence of autoimmune thyroiditis, micropapillary carcinoma nor any other malignancy.

OUTCOME AND FOLLOW-UP

The patient had an uneventful recovery and is now on thyroxine replacement. The patient and her partner are undergoing genetic counselling in order to plan starting a family.

DISCUSSION

Pendred syndrome was first described by Vaughan Pendred in 1896, after noting the coincident combination of hearing loss,

mutism and goitre in an Irish family.¹¹ It is an autosomal recessive inherited disorder, which may be accompanied by a goitre associated with sensorineural hearing loss.¹²

One hundred years later, in 1996, the gene responsible for Pendred syndrome was discovered and mapped to chromosome 7q31.^{13 14} The gene, *SLC26A4*, codes for the protein pendrin (PDS), a chloride-iodide cotransporter found in the thyroid, inner ear and kidney.¹⁵ In the thyroid, pendrin transports iodide out of thyrocytes to allow for iodination of thyroglobulin. Mutated pendrin results in less iodide transported out and causes reduced organification of thyroglobulin, and goitre may form, though this is dependent on iodine intake.¹⁵ Pendrin in the kidney is found in the apical membrane in intercalated cells in the cortical part of collecting ducts and plays a role in renal bicarbonate secretion.¹⁶ In the inner ear, pendrin is expressed in the endolymphatic duct and sac where it functions as a chloride/bicarbonate exchanger and plays a role in fluid transport and generation of the endocochlear potential.¹⁷ Pendrin is necessary for auditory and vestibular function and appears to be required for the normal development of inner ear structures.¹⁸ Over 150 pathogenic variants in the pendrin gene have been found, ranging from mainly missense mutations to nonsense, splice site and frameshift mutations.¹⁷

Clinical presentation of Pendred syndrome can vary. Sensorineural hearing loss is often prelingual and profound, however it can fluctuate, developing later on in life, sometimes following on from a head injury.^{17 19} A congenital goitre may be apparent and prompt the diagnosis, but some cases may have no thyroid enlargement at all.^{12 20} This varying clinical presentation can make diagnosis difficult, perhaps underestimating the prevalence of the syndrome.

The perchlorate discharge test unmasks organification of iodide defects by provoking discharge of inorganic iodide from the thyroid gland.²⁰ It is the gold standard investigation for Pendred syndrome. However, it is not specific to the syndrome and imaging with MRI has recently become more frequently employed to support the diagnosis. In one study, over 80% of familial cases of Pendred syndrome demonstrated structural malformations of the cochlea, identifiable by CT scan.¹² Another study found MRI imaging to be 83.6% sensitive in detecting patients with Pendred syndrome.²¹ The Mondini malformation of the cochlea is not specific to Pendred syndrome, but is often present. The interscalar septum in the distal coils is deficient.²² Instead of 2.5 turns in the normal cochlear spiral, there is a hypoplastic coil of 1.5.¹² There may also be dilated vestibular aqueducts.

Profound congenital hearing loss is estimated to occur in about 1–2 in 1000 births.²³ Approximately 50% of cases are thought to be due to environmental factors and the remainder due to genetic causes. In cases associated with genetic factors, 30% have one of more than 400 forms of syndromic hearing loss, which may be diagnosed because of associated clinical findings, while 70% have hearing loss not associated with other clinical findings.²³ More than 80 hearing loss genes, with more than 1200 mutations, have been identified, making it one of the most genetically heterogeneous traits.²⁴ Advances in next-generation sequencing gene panel testing are now increasingly used to enable prompt, cost-effective and reliable genetic diagnoses to be made.^{23 24} Recent guidelines advise that following a detailed medical history (including birth history), family history, physical examination and audiometric assessment, genetic testing should be considered in cases of acquired hearing loss.²³

When combined with the clinical features, the non-specific tests discussed previously can provide evidence pointing towards

a diagnosis of Pendred syndrome, however, molecular diagnosis can be used to detect whether a pathogenic variant is present in the *SLC26A4* gene and confirm the presence of Pendred syndrome.

Learning points

- ▶ Clinical presentation varies. Our case highlights that goitre may present late or not at all, alongside normal thyroid function tests.
- ▶ Goitre combined with a history of hearing loss should evoke suspicion of Pendred syndrome. MRI of the auditory canals can aid in supporting these suspicions, and molecular testing can confirm diagnosis.
- ▶ Sensorineural hearing loss, though often prelingual and profound, can fluctuate and develop later on in life, sometimes following on from a head injury. It can also be associated with vestibular dysfunction.
- ▶ There is no specific treatment or cure for Pendred syndrome. Thyroid hormone deficiencies can be supplemented. Contact sports or situations that could cause head injury are best avoided to prevent further hearing loss. Speech and language therapy and cochlear implants can be offered. Genetic counselling can be offered to those planning a family.

Contributors NS, J-MU-K-I and JK wrote the manuscript. J-MU-K-I and JK involved in the care of the patient.

Competing interests None declared.

Patient consent Obtained.

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