Pendred syndrome in Tunisia

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Pendred; Deafness; Goiter; Enlarged vestibular aqueduct

Summary
Objectives: We report a clinical and genetic study of three consanguineous Tunisian families affected by Pendred syndrome.

Patients and methods: Three families from the south of Tunisia were identified as affected by Pendred syndrome. The patients and their families underwent ENT and general examination and audiovestibular and radiological tests. Molecular DNA analysis was performed by the Sfax Human Molecular Genetics Department.

Results: Forty-three patients (mean age: 21 years [2—60 years]) were affected. Tonal audiometry showed bilateral sensorineural hearing loss in 87.5% of cases, and mixed hearing loss in 12.5% with bilateral high frequency sensorineural hearing loss and conductive hearing loss at lower frequencies. Deafness was severe in 21% and profound in 79% of cases. Thyroid goiter was found in 46.5% of cases. Inner ear CT scan found enlarged bilateral vestibular aqueducts in all cases. Hormone analysis was normal and perchlorate test negative in all cases. A single Pendred syndrome (PDS) gene mutation, L445W, was found.

Discussion: Pendred syndrome is the most frequent congenital deafness syndrome. It is characterized by great intrafamilial phenotype variability.

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Introduction
Pendred syndrome (PS), associating sensorineural hearing loss, inner ear bone malformation and thyroid goiter, is the most frequent of congenital deafness syndromes. It is a clinically and genetically heterogeneous recessive autosomal genetic disorder.

Few studies worldwide, and none so far in Tunisia, have analyzed its clinical characteristics. A relationship between sporadic goiter and hearing loss was first mentioned in 1824 [1], but Pendred first suggested its familial nature in 1896, on the basis of an observation of two deaf-mute sisters with pronounced goiter [2]. Morgans and Trotter, in 1958 [3], and Fraser, in 1965 [4], showed partial thyroxin synthesis deficit in organic incorporation of iodine to underlie the goiter formation. The PDS gene (Pendred syndrome gene), now known as SLC26A4, is involved in
the genesis of PS, with more than 140 mutations currently described.

We report a clinical and genetic study of three carrier families, from southern Tunisia.

Patients and methods

Clinical study

The Sfax ENT team’s study of familial hearing loss was essentially based on fieldwork with affected families. In each mission, the team comprised two ENT physicians, two geneticists and one cochleovestibular exploration technician. Three families in southern Tunisia were thus identified as PS carriers.

Interview ruled out acquired hearing loss and detailed each family’s history of hearing impairment, with clinical and evolutive characteristics, and drew up family trees. Clinical ENT examination of all family members comprised otoscopy and vestibular, mouth cavity and dental, rhinological, cervical and general examination.

Auditory exploration comprised pure tone audiometry (PTA) via headphones at 250, 500, 1000, 2000 and 4000 Hz to determine hearing loss frequency, threshold and Rinne; mean hearing threshold and mean Rinne were calculated for both ears.

Vestibular exploration comprised bithermal caloric test using water at 30° and 40°C, with results displayed on a Freyss’ graph; reflectivity, valence and preponderance were calculated.

Certain family members were admitted to our department for complementary cochleovestibular, biological and CT exploration.

Genetic study

DNA molecular analysis was performed by the Sfax human molecular genetics team.

Results

Clinical results

Three carrier families were identified, in the Ben Guerdène and Tataouine governorates of southern Tunisia. The total number of affected subjects was 43, with a mean age of 21 years (range: 2–60 years) and 18.6% under the age of 10 years. The sex ratio was 0.65 (predominantly female). Fig. 1 presents the genealogical trees of the three families.

Neck palpation found goiter in 46.5% of cases: diffuse in 58% and nodular in 42%. 62.5% of the under 10-year-olds had diffuse thyroid goiter. Eighty percent of the nodular goiters were in patients over 30 years of age.

PTA was performed in 40 cases and found bilateral perceptual hearing loss in 87.5% of cases; the remaining 12.5% showed mixed, predominantly bilateral sensorineural hearing loss, with a mean Rinne of 25 dB (range: 10–40 dB). Hearing loss was symmetric in 85% of cases (n = 34), severe in 21% and profound in 79% (Fig. 2). Onset was very early and always severe or profound. All and especially high frequencies were involved, without any obvious fluctuation.

Figure 1  Genealogical trees of the three families.
Caloric examination was performed in 19 cases and found vestibular hyporeflexivity in 47%, areflexivity in 42% and directional preponderance in one case. Only one of the 19 patients had normal results.

Inner ear CT scan was performed in eight cases and found bilateral vestibular aqueduct enlargement in all eight (Fig. 3).

Hormone assessment and thyroid scans were normal. Perchlorate test was performed in eight cases, all negative.

Genetic results

A single PDS gene mutation was found systematically in the three families: L445W, a thymine to guanine transversion in exon 11 at position 1558 (1558 T → G). The relevance of this mutation has been demonstrated.

Discussion

More than 300 genetic syndromes involving hearing loss have now been described [5]. With an incidence of 7—10/100,000 births [6], PS accounts for 2 to 10% of cases of hearing loss syndrome. To the best of our knowledge, incidence has not been specified for North Africa, Africa or the Arab countries.

Clinically, PS associates sensorineural hearing loss and goiter, with wide phenotype variability.

Hearing loss is typically cochlear, prelingual or early postlingual, with various evolutions. It may be immediate [1] or evolve in sudden steps followed by partial recovery, as in fluctuating hearing loss [7]. According to Boniver [1], it is typically perceptual and predominantly high-frequency; according to other authors, it is mixed, with perceptual predominance and a transmissional low-frequency component [8,9]. The present series presented two types of audiometric curve: pure perceptual hearing loss predominating at high-frequencies (87.5%), or mixed with low-frequency Rinne (12.5%). In terms of evolution, in the present series hearing loss was permanent, with no signs of fluctuation or stepwise deterioration. Onset was very early and immediately severe or profound in all cases.

Several authors reported clinical signs of vestibular involvement [7,10], while others reported normal vestibular function [1]. In the present series, no patients showed vestibular signs although the caloric test was normal in only one case, showing vestibular hyporeflexivity in 47% of cases, areflexivity in 42% and directional preponderance in one case.

Eighty percent of cases showed abnormal inner ear morphology, almost always in the form of enlarged vestibular aqueduct or Mondini dysplasia [11]. Johnsen et al. [12] found Mondini dysplasia in all of six inner ears of Pendred carriers. Goldfeld et al. [11], in a radiological study, found no superior turn of the cochlea in 75% of cases, enlarged vestibular aqueduct in 80%, and modiolus deficiency in 100%. For several authors, enlarged vestibular aqueduct is the characteristic feature of PS, corresponding to a PDS gene mutation [10,13]. It is bilateral in 80% of cases [11]. In the present series, bilateral enlarged vestibular aqueduct was found systematically.

Thyroid signs are highly variable, hindering the establishment of diagnostic criteria [14]. Goiter is caused by iodine incorporation disorder with incomplete thyroxin synthesis [1], and prevalence is inversely proportional to daily iodine intake [15]. Onset is usually (63%) towards the end of the first decade or in young adulthood [16], but it can sometimes be present at birth [1]. Both sexes are affected [16]. It is first soft and diffuse, then hard and nodular [1] and sometimes compressive [11]. In the present series, it was found in 62.5% of children under the age of 10 years.

Thyroid function is likewise variable. Hypothyroidism was reported in 44 to 77% of goiters [16,17], sometimes at birth [18].

The perchlorate diagnostic test, introduced by Morgans and Trotter in 1958 [3], is based on salting out of non-incorporated radioactive iodine by perchlorate ions and therefore reducing thyroid radioactivity following perchlorate absorption. Results were systematically negative in the
present series, casting doubt on the test's sensitivity and specificity for PS. It also shows positive in Hashimoto thyroiditis, peroxidase deficiency and radioactive iodine-131 therapy [19], and has therefore given way to molecular and genetic diagnosis for PS [20].

Hormone substitution is recommended in case of hypothyroidism; total thyroidectomy is rarely indicated [15].

Histologically, no characteristic aspect has been identified, and no malign transformation reported [1].

The PDS gene or SLC26A4, underlying PS, lies in the 7q31 region of chromosome 7 and codes for pendrin, a 86-kDa transmembrane polypeptide containing 780 amino acids, largely expressed in the inner ear and thyroid [21]. It is critical to endolymphatic fluid homeostasis [22].

As well as PS, PDS gene mutation may cause DFNB4 congenital recessive deafness and enlarged vestibular aqueduct syndrome. Only the thyroid goiter distinguishes the two types of hearing loss, but intrafamilial variability in thyroid involvement greatly hinders differential diagnosis.

More than 140 PDS mutations have been reported [13], each involving a different pendrin protein, with differing metabolic and phenotypic impact [23]. Phenotypic variability within a given family showing a single mutation, however, remains to be explained, and may indicate the involvement of other genetic factors [24].

In the present series, a single mutation, UW445 [25], also reported in the Netherlands [26] and in Spain [27], was found in all three families.

Conflict of interest statement

The authors have not communicated conflicts of interest.

References