Original papers

Pendred syndrome—100 years of underascertainment?

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Summary

Pendred syndrome is an autosomal recessive condition classically characterized by deafness and goitre. Since both cochlear and thyroid pathology are required to secure the diagnosis, it is unclear whether the condition might present without the classical features. The perchlorate discharge test, the gold-standard investigation for Pendred syndrome, is non-specific. and in the absence of alternative means of confirming the diagnosis, its sensitivity is unknown. We used the recent mapping of the gene to chromosome 7q to identify pedigrees with a likely diagnosis of Pendred syndrome, and assessed the prevalence of clinical parameters of disease in affected patients. Thirty-six familial cases showed co-segregation between disease and the Pendred syndrome locus on chromosome 7q. Clinical and investigative findings were compared in index cases ($n=18$) vs. affected siblings ($n=18$). The overall prevalence of goitre was 73%, higher in index cases (94%) than in siblings (56%), many of whom had not previously been considered to have the condition. One perchlorate discharge test was false-negative (2.9%). Radiological malformations of the cochlea were identified in 86% of cases. Securing a diagnosis of Pendred syndrome may be difficult, especially in the single case. The perchlorate discharge test, although valuable, is difficult to undertake in the younger patient, and radiology may assist in diagnosing such patients.

Introduction

Congenital deafness is common, affecting 1:1000 births.\textsuperscript{1} Defining an exact aetiology for the deafness is often not possible, but long-term follow-up of families with congenital deafness suggests that at least 50% of cases have a genetic cause.\textsuperscript{2,3} Most of the inherited forms of deafness are clinically indistinguishable, the pathology being confined to the cochlea. These conditions are termed non-syndromic deafness, and represent a highly heterogeneous group with autosomal-dominant, autosomal-recessive and X-linked forms described.\textsuperscript{4} The numerically less common syndromic forms of inherited deafness,
thought to represent about 30% overall, involve pathology in other organ systems outside the cochlea, thus offering a clinical basis for identification of genetically distinct conditions. One such condition is Pendred syndrome, in which deafness is associated with goitre and thyroid disease. In the only study of its type, Fraser calculated that this particular disorder accounted for 7.5% of all congenital deafness. If these data are truly representative, then Pendred syndrome would be the single most common cause of congenital deafness. Contemporary studies into the aetiology of congenital deafness do not support a major causative role for Pendred syndrome. Indeed, modern studies are striking for the relative paucity of cases of Pendred syndrome identified. Difficulties in the clinical definition of Pendred syndrome underlie this apparent discordance in prevalence between different studies, and prompt a need for re-evaluation of the condition in the context of recent developments in the molecular genetics of Pendred syndrome.

Securing the diagnosis of Pendred syndrome is important, not just in terms of management of the thyroid dysfunction, but also for genetic counselling purposes. This is especially true in the singleton case, where the identification of the syndrome would clearly signal the 25% recurrence risk applicable to the couple, compared with the 10% empiric recurrence risk usually advised to the parents of a single deaf child for whom no specific diagnosis has been made.

Originally reported as familial deafness and goitre, Pendred described his observations in two sisters from a sibship of 10 in 1896. Brain reported further sibships and recognized the autosomal recessive inheritance of the condition. The diagnostic criteria in these early reports were the observation of both deafness and goitre in the absence of iodine deficiency. Arising from the observation of inappropriate iodide release by the thyroid on perchlorate challenge in an affected sibship, Fraser used the perchlorate discharge test in several of the families included in his survey. This addition to the diagnostic criteria for Pendred syndrome resulted in the recognition of a wide variability in the degree of thyroid involvement, ranging from congenital goitre to the complete absence of thyroid enlargement. However, the perchlorate discharge test is not specific to Pendred syndrome, abnormal thyroid response also being recognized in Hashimoto’s thyroiditis, total iodide organification deficiency (TIOD) and 131I-treated thyrotoxicosis.

With respect to audiological evaluation, basic audiometric findings in Pendred syndrome are non-specific. Hence some authors have advocated the use of CT scans of the cochlea, specifically to demonstrate a Mondini malformation of the cochlea as an aid to diagnosis. This eponymous interruption of cochlear development involves normal formation of the basal coil of the cochlea with failure of differentiation of the latter one and threequarter cochlear turns. However, the Mondini malformation of the cochlea represents a causally heterogeneous radiological observation, and is of limited diagnostic value as a sole finding. Such data as exist on Mondini malformation in Pendred syndrome are observations made in confirmed cases of the syndrome, and do not address the question of what proportion of Mondini malformations are likely to be caused by Pendred syndrome. Hence, the fundamental problem in the identification of Pendred syndrome, the non-specificity of the investigations, is not resolved by the addition of radiological criteria.

The gene for Pendred syndrome has recently been localized to chromosome 7q by two independent groups. In our UK-based study of Pendred syndrome, we have identified 36 familial cases, enabling a reconsideration of current protocols for the investigation and diagnosis of the condition. Since all cases support linkage to the same region of chromosome 7q, concerns with respect to the homogeneity of our patient population have been overcome. Our experience suggests a significant underascertainment of Pendred syndrome among deaf patients.

Methods

In total, 28 probands (age range 5–53 years) were referred by audiological, endocrine and genetic colleagues with various combinations of deafness and thyroid anomaly. Of these patients, 10 represented single cases in their families, and were excluded from the familial study. Investigation of the remaining 18 probands led to the identification of 36 affected familial cases from the 18 kindreds. Molecular analysis in these families, using a panel of microsatellite DNA markers from the region of chromosome 7q31 known to define the Pendred syndrome locus, showed cosegregation of haplotypes between affected individuals. These 18 families form the cohort reported here, and the molecular confirmation of Pendred syndrome has enabled us to evaluate clinical criteria for the diagnosis of Pendred syndrome in the index cases (n=18) as opposed to the affected sibling group (n=18). The 36 cases upon which this report is based comprise 18 probands and exactly one sibling for each proband.

Patients were assessed by clinical examination, including palpation of the thyroid, detailed audiological and vestibular function studies, CT scan of the petrous temporal bone, the perchlorate discharge test and thyroid function tests (T4 and TSH), including...
autoantibodies. Deafness is the clinical feature common to all. A positive perchlorate discharge test was defined as a discharge of greater than 10% of radiiodide from the thyroid in response to perchlorate provocation.\textsuperscript{10,18}

Results

Of the 36 familial cases, 27 (73.3%) had evidence of goitre on clinical examination, of which five had been objectively recorded before the age of 10 years. A further five developed goitre around the time of puberty, but in the majority of cases, (17/27, 62.9%) the initial documentation of goitre was in early adult life. There was no familial pattern to the development or otherwise of goitre. Goitre was present in 17/18 index cases (94.4%) but in only 10/18 (55.5%) affected siblings (Table 1). While 21 patients were started on thyroxine following the diagnosis of goitre, only 3/27 (11.1%) patients had abnormal thyroid function as identified by a raised serum TSH (>5 mU/l). There was no instance of abnormal thyroid function in the absence of goitre. Notwithstanding the oral thyroxine medication, 12/27 cases with goitre (44.4%) came to surgery.

Perchlorate discharge tests were undertaken in 35 cases. In 18/18 (100%) index cases and 16/17 (94.1%) siblings, there was abnormal discharge of iodide by the thyroid on perchlorate challenge. There was one false negative in the sibling group, a false-negative rate of 5.9% in this group (Table 1) and 2.9% in the study overall (1/35 tested). Levels of discharge in affected individuals varied from 21% to 72%. There was no concordance between siblings with respect to response to perchlorate (Figure 1).

All patients had bilateral, essentially symmetrical sensorineural hearing impairment, generally of prelingual onset. In addition to the hearing problems, up to 66% of patients surveyed had objective signs of vestibular dysfunction. A range of disturbance was seen, from mild unilateral canal paresis to gross bilateral absence of function.

Radiological evaluation of the petrous temporal bones was abnormal in 31 (86.1%) (16 probands, 15 siblings) of the 36 familial cases. Abnormalities ranged from bilateral dilatation of the vestibular aqueducts through to a frank Mondini malformation of the cochlea with resultant gross cochlear malformation (Figure 2); five patients had normal radiology. These five patients comprised two proband and sibling pairs, and one sibling. Moreover, there were five instances of intrafamilial discordance between index case and sibling with respect to radiological appearance, but in only one of these instances was the radiology abnormal in an index case (dilated vestibular aqueduct) and normal in the sibling. The other four instances of discordance comprised Mondini malformation in one of the sibling and dilated vestibular aqueducts in the other.

Table 1: Clinical features in the siblings of Pendred syndrome index cases

<table>
<thead>
<tr>
<th>Age</th>
<th>Deaf</th>
<th>Abnormal</th>
<th>Goitre</th>
<th>TSH</th>
<th>Perchlorate</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>N</td>
<td>21%</td>
</tr>
<tr>
<td>20</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>N</td>
<td>60%</td>
</tr>
<tr>
<td>22</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>N</td>
<td>50%</td>
</tr>
<tr>
<td>20</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>N</td>
<td>40%</td>
</tr>
<tr>
<td>18</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>46%</td>
</tr>
<tr>
<td>16</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N</td>
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</tr>
<tr>
<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>34%</td>
</tr>
<tr>
<td>18</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>45%</td>
</tr>
<tr>
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<td>+</td>
<td>+</td>
<td>–</td>
<td>N</td>
<td>25%</td>
</tr>
<tr>
<td>24</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>59%</td>
</tr>
<tr>
<td>22</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>TSH30</td>
<td>59%</td>
</tr>
<tr>
<td>8</td>
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<td>+</td>
<td>–</td>
<td>N</td>
<td>21%</td>
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<td>30</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N</td>
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<tr>
<td>22</td>
<td>+</td>
<td>–</td>
<td>+</td>
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<td>40</td>
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<td>+</td>
<td>+</td>
<td>N</td>
<td>8%</td>
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<td>–</td>
<td>+</td>
<td>N</td>
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</tr>
<tr>
<td>48</td>
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<td>–</td>
<td>N</td>
<td>59%</td>
</tr>
<tr>
<td>35</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>N</td>
<td>ND</td>
</tr>
</tbody>
</table>

N, normal; ND, not done; +, present. TSH, thyroid-stimulating hormone.

Discussion

The data we report represent a unique investigational profile of Pendred syndrome, as they are derived from a homogeneous cohort of patients with evidence of linkage to chromosome 7q31. Our observations clearly identify the underascertainment which follows the application of clinical criteria alone for the diagnosis of the disorder. Among our index cases, 17/18 (94.4%) had deafness and goitre, while in the sibling group only 10/18 (55.5%) satisfied these diagnostic criteria. This observation highlights the potential for underascertainment, and is supported by the fact that only 5/36 cases we report here had been recognized as cases of Pendred syndrome at the outset of the study.

While hearing impairment continues to be a \textit{sine qua non} of the diagnosis of Pendred syndrome, the variability both in the degree of impairment and the clinical presentation is a previously unrecognized feature. Four patients showed progressive post-lingual deterioration of hearing following head injury. These findings contrast with the mainly prelingual profound hearing loss associated with Pendred syndrome as identified in previous studies, and which has
Figure 1. Perchlorate discharge test results in a pair of siblings with Pendred syndrome. Top, 60% discharge in response to perchlorate challenge in a 22-year-old patient; below, his 24-year-old sister, discharge level of 27%. The X-axis represents time and the Y-axis shows the activity generated within the thyroid gland by the radiolabelled iodine.

Figure 2. Axial CT scan of the petrous temporal bone in a patient with Pendred syndrome to show a typical example of Mondini malformation (arrowed). Only the basal cochlear coil is well-formed.

influenced our former profile of the presentation of the disorder. Likewise, the variability in goitre/thyroid involvement, while previously observed, further emphasizes the difficulty which currently attends clinical definition of this syndromic form of deafness. The absence of a specific biochemical marker for the disease, and the findings of our study necessitate a reassessment of the clinical investigation of the deaf patient. Our work clearly reiterates the value of the perchlorate discharge test in supporting the diagnosis of Pendred syndrome. Since this has been an essential prerequisite of the diagnosis up until now, it has not been possible to evaluate the false negative rate which might attend that investigation.
The single case we identify in our cohort of siblings suggests that occasional false negatives should be anticipated. If this is so, the scope for further under-ascertainment of Pendred syndrome is even wider. Resolution of the sensitivity of the perchlorate discharge test in Pendred syndrome must await further development in the molecular genetics of the condition. Nevertheless, on current evidence, perchlorate discharge testing remains an essential element of the investigation and diagnosis of the disorder. We propose that perchlorate discharge testing should form an essential element of the investigation of the singleton deaf child, particularly where issues of recurrence risk arise in genetic counselling. Only 7/33 nuclear medicine departments responding to an enquiry from us had received a request to perform this investigation in the last 10 years. The test is not easily undertaken in the younger child, and perhaps it is in this context that our radiological findings are most valuable.

In excess of 80% of our familial cases had structural malformation of the cochlea identifiable by CT scan. While no data exist to determine what proportion of these malformations may be directly attributable to Pendred syndrome, many deaf patients are now routinely investigated by radiological means with a view to assessing suitability for various forms of management. Our data support an argument for proceeding to perchlorate discharge test, particularly in those cases with radiological manifestations of Mondini and related malformations, including those of dilated vestibular aqueduct.

Ultimately, resolution of the diagnostic conundrum represented by Pendred syndrome may be facilitated through the identification and characterization of the genetic basis of the condition. At that time, prevalence studies within the deaf population on the basis of molecular and clinical investigations should substantially resolve the issue of the relative contribution of Pendred syndrome to genetic deafness.

Acknowledgements

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References