TYPICAL AND ATYPICAL CASES OF PENDRED'S SYNDROME IN ONE FAMILY

By

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ABSTRACT

Pendred's syndrome is a condition which, in its complete form, is characterized by congenital deaf-mutism, goitre, and defective organic binding of iodide in the thyroid. However, there are less typical cases, e.g. without a goitre, with only limited hearing loss, or a normal perchlorate discharge test.

A family was studied in which Pendred's syndrome was found in two generations. The complete form was present in two members; two other members were considered to show less typical forms of the same disorder. All were euthyroid. Three out of five sons were deaf-mute and goitrous. Perchlorate caused a discharge of radioiodine from the thyroid in two of them, and also in the father who had no goitre and a slight loss of hearing only detectable by audiometry.

Peripheral deiodination of radioactive diiodotyrosine was normal in all patients, but had been abnormal in one son while he was hypothyroid.

The combination of deafness and thyroid disorder appears in endemic cretinism (De Quervain & Wegelin 1936), adult myxoedema (Wayne 1960) and Pendred's syndrome.

Pendred (1896) described the combined occurrence of sporadic goitre and congenital deafness. Morgans & Trotter (1958) found a disturbed organic binding of iodine in the thyroid of patients with Pendred's goitre-deafness syndrome. The incidence of the syndrome is estimated at 1 to 5 per 100 000 inhabitants (Thould & Scowen 1961; Fraser 1964). The goitre is initially diffuse and later on mostly nodular. Its weight may be anything from normal (hardly palpable) to over 200 grams (Fraser et al. 1960). The onset of the goitre mostly occurs at the time of puberty (Fraser et al. 1960), though some-
times the goitre is already present at birth (Nilsson et al. 1964). Unless adequate therapy with thyroxine is given, the goitre generally increases in size, showing a marked tendency to recur following partial thyroidectomy, so that many patients have been operated on more than once, sometimes three or four times (Fraser et al. 1961; Nilsson et al. 1964).

Most patients are euthyroid and suffer from a serious deafness, resulting in deaf-mutism. The deafness is not the result of hypothyroidism (Fraser 1965; Bax 1965). The uptake of radioiodine is mostly high. A perchlorate discharge test induces a decrease of 15 to 80% of the neck activity (Fraser et al. 1960).

Pendred’s syndrome is a recessive hereditary disease (Fraser 1964, 1965). In only some families does the syndrome occur in two or more generations (Johnsen 1958; Baschieri et al. 1963; Fraser 1964, 1965; Malamos et al. 1964).

MATERIAL, METHODS AND RESULTS

Of a family (Fig. 1, Table 1) living in an area in which goitre is not endemic, all members were euthyroid; three sons were goitreous and deaf-mute and two sons were normal. The non-goitreous father, though unaware of a hearing defect, had a hearing loss for high tones. Four sibs of the father were normal; the eldest brother of the father, the sibs of the mother and the grandparents, who could not be investigated, were said to be normal.

PBI was determined by the technique of Barker et al. (1951); BEI by a modification of the method of Man et al. (1951). PBI and BEI of the parents and their sons were in the normal range. Radioiodine was administered orally and thyroid uptake was determined one hour later. Two of the goitreous sons had a high uptake. One hour after the administration of radioiodine, 400 mg potassium perchlorate was given orally and the activity in the thyroid was measured again, half an hour and one hour later. Perchlorate caused a decrease in the thyroid activity in the father and two of the goitreous sons (Table 1).

For a determination of the peripheral deiodinating capacity, 5µc radioactive DIT (specific activity about 1µc/µg) was injected intravenously into the parents and their sons (excluding the youngest). The urine was collected one and two hours later and chromatographed in butanol acetic acid (Wiener & Lindeboom 1964). The same investigation was carried out in two healthy volunteers. 3 to 11% of the 131I in the two samples of urine from each patient was found to be unchanged DIT, the remainder being iodide. Similar values (3 to 9%) were found in the control subjects.

Five years previously the same investigation had been done in son 3. Radio-DIT was injected intravenously, and 75% of the 131I in the patient’s urine after two

Abbreviations used:

PBI = protein-bound iodine
BEI = butanol-extractable iodine
MIT = monoiodotyrosine
DIT = diiodotyrosine
CPS = cycles per second
DB = decibel

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hours was shown to be unchanged DIT. This together with clinical and laboratory evidence (PBI 0.7 µg/100 ml) suggests that at that time he was hypothyroid.

Air-conduction and bone-conduction audiograms were recorded on a standard Pedersen apparatus.

**DISCUSSION**

Initially, the diagnosis of what was later called Pendred’s syndrome was established on the basis of the (familial) co-existence of sporadic goitre and congenital perception deafness. After the studies by Morgans & Trotter (1958) the disturbed organic binding should be considered of major importance, and actually is indispensable in nearly all cases for the establishment of the diagnosis.

Thus, Pendred’s syndrome in its complete form is characterized by congenital deaf-mutism, goitre, and defective organic binding of iodide in the thyroid. However, there are less typical forms. Goitre may be absent (Von Harnack et al. 1961; Fraser 1965) and in some instances, the auditory disturbance is very slight or only demonstrable by audiometry (Fraser et al. 1961; Fraser 1964). If, on the other hand, the perchlorate test in a deaf and goitrous patient is normal, the diagnosis of Pendred’s syndrome is, in our opinion, not proved unless one or more members of the family display the complete form of syndrome. Though rare, there are cases of co-existent (familial) sporadic goitre and deafness without disturbance in the organic binding.
Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Thyroid size*</th>
<th>Age at onset of goitre</th>
<th>Deaf-mutism</th>
<th>Hearing loss in DB**</th>
<th>PBI serum μg/100 ml</th>
<th>131I uptake (1 hour) % of dose</th>
<th>Percentage of fall after KClO₄ (% initial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>43</td>
<td>±</td>
<td>—</td>
<td>—</td>
<td>0/30</td>
<td>3.9</td>
<td>24/32</td>
<td>41/32</td>
</tr>
<tr>
<td>Mother</td>
<td>36</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>0/0</td>
<td>3.8</td>
<td>20/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Son 1</td>
<td>10</td>
<td>0</td>
<td>—</td>
<td>0/10</td>
<td>70/100+</td>
<td>3.9</td>
<td>61/27</td>
<td>0/0</td>
</tr>
<tr>
<td>Son 2</td>
<td>9</td>
<td>++</td>
<td>1</td>
<td>+</td>
<td>70/100+</td>
<td>3.9</td>
<td>61/27</td>
<td>0/0</td>
</tr>
<tr>
<td>Son 3</td>
<td>7</td>
<td>++</td>
<td>1</td>
<td>+</td>
<td>70/100+</td>
<td>4.7</td>
<td>33/2</td>
<td>2/0</td>
</tr>
<tr>
<td>Son 4</td>
<td>5</td>
<td>++</td>
<td>1</td>
<td>+</td>
<td>50/90</td>
<td>5.9</td>
<td>47/26</td>
<td>36/0</td>
</tr>
<tr>
<td>Son 5</td>
<td>1</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>0/0</td>
<td>—</td>
<td>—</td>
<td>0/0</td>
</tr>
</tbody>
</table>

*0 = thyroid not palpable; ± = just palpable; + = well palpable; ++ = goitre.

**) Mean loss for the right and left ear.
in which the diagnosis Pendred's syndrome is thus not justifiable (Fraser et al. 1960; Von Harnack et al. 1961; Hollander et al. 1964). We have studied 7 children, three of whom were sibs, who had a (familial) sporadic goitre and a congenital perception deafness (with the maximal loss of hearing for high tones) but in whom the perchlorate test proved normal (Bax 1965). Thus, in these children, the diagnosis of Pendred's syndrome could not be established. This diagnosis has also not been proved in many patients, e.g. in 270 out of the 334 patients of Fraser (1965) and in 6 out of the 23 patients of Thould & Scowen (1961), in whom a perchlorate test was not performed. Thould & Scowen (1964) considered two isolated cases with sporadic goitre, congenital deafness and a normal perchlorate test as suffering from Pendred's syndrome, which in our opinion is not justifiable.

However, it should be taken into account, that there is evidence that sometimes a slight disturbance in the organic binding may not be demonstrable by the perchlorate test (Cottino et al. 1959; Lelong et al. 1960; Malamos et al. 1964). Hence, there may be some cases of the goitre-deafness syndrome in which a normal perchlorate test is found. However, this statement should not be used indiscriminately.

In the family reported here (see pedigree) we found Pendred's syndrome, a recessive hereditary disease, in two generations. The complete form was present in two members, son 2 and 4; two other members, the father and son 3, were considered to display less typical forms of the same disorder. Three out of five sons were deaf-mute and goitrous. All were euthyroid. Perchlorate caused a discharge of 31 and 36 %, respectively, of the activity over the neck in two of the goitrous sons (Table 1). In the third, the result of the test was normal, but no other cause than Pendred's syndrome was found for the goitre and deaf-mutism. This patient had not suffered from a disease causing hearing loss. Inability of the thyroid to trap iodide and defective (peripheral) deiodination of iodotyrosines was excluded, and there was no evidence of abnormal iodinated proteins or peptides in the serum. Although other inborn errors of iodine metabolism could not be excluded, it seems improbable that his goitre and deaf-mutism were not related to the genetic abnormality affecting his family.

The father had a good sense of hearing, and his thyroid gland was not enlarged. However, 41 % of the activity over the neck was discharged by perchlorate. An audiogram showed a loss of hearing of 30 db at 3000 cps; so he was not deaf but he had a slightly disturbed hearing in the high tones (he had no noise-dip).

The mother and the two other sons had normal thyroid glands, and the perchlorate tests and audiograms were normal; this was also found in the brothers and sisters of the father.

In the determination of the peripheral deiodinating capacity in normal
subjects, Stanbury et al. (1956 a) found 2 to 27 % of the $^{131}$I unchanged DIT in the urine collected one and two hours after intravenous administration of radio-DIT. In patients with a deiodinase defect, more than 90 % of the $^{131}$I excreted was found to be unchanged DIT (Stanbury et al. 1956 b). In one of the goitrous sons (son 3) a diminished peripheral deiodination capacity had been found five years previously. At that time, 75 % of the $^{131}$I in the urine collected two hours after i. v. radio-DIT was incorporated in unchanged DIT, indicating the presence of a partial deiodination defect. This was found, together with clinical and laboratory evidence (PBI 0.7 µg/100 ml) suggesting that at that time he was hypothyroid. At present he, as well as the other members of the family, show a normal peripheral deiodination capacity of radio-DIT (less than 11 % of the $^{131}$I, excreted after one and two hours, being found to be unchanged DIT). McGirr (1960) discussed some hypothyroid patients (investigated by Werner et al. 1957; Mosier et al. 1958; Gardner et al. 1959) in whom there seemed to be a combination of an iodotyrosyl coupling defect and a partial deiodination defect, and postulated that an excessive accumulation in the thyroid of MIT and DIT in conjunction with a hypothyroid state may overwhelm a fundamentally normal dehalogenase system, which is temporarily at a disadvantage. Haddad & Sidbury (1959) and Gardner et al. (1959), however, presented some hypothyroid patients with a diminished ability to deiodinate radio-DIT and an organification defect, in whom one would not expect an excess of iodotyrosines to be produced by the thyroid. These patients and also the case (son 3) described here, give suggestive evidence, that they have a partial deiodination defect, present in and only resulting from a hypothyroid condition. After restoration of the euthyroid state, son 3 had a normal peripheral deiodination capacity; this was also found by Mosier et al. (1958).

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