Congenital hypothyroidism from complete iodide transport defect: long-term evolution with iodide treatment

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Summary: Hypothyroidism from iodide transport deficiency is a rare disease, especially when found in two affected siblings. Treatment with high doses of iodide has been recommended, but no long term results have been reported.

Two siblings with congenital hypothyroidism due to total failure to transport iodide have been followed up during twelve and a half years of treatment with oral potassium iodide.

Iodine doses varied between 10.3 and 22 mg/day, and serum total iodine concentrations between 100 and 210 μg/dl. Total triiodothyronine (T₃), thyroxine (T₄) and free T₄ were in the normal range during the time of study. Basal thyroid stimulating hormone (TSH) and maximum TSH response to thyrotrophin releasing hormone (TRH) were also in the range of normal values. These data along with clinical findings confirmed the potential usefulness of iodine in hypothyroidism due to complete iodide transport defect.

Introduction

Among the different types of congenital hypothyroidism due to an alteration in thyroid hormone biosynthesis described by Stanbury & Dumont,¹ one of the less frequent is that originating from the failure of the thyroid cell to transport iodide. In this case, the gland loses the capacity to concentrate iodide against chemical and electrical gradient. This lowers the glandular content of iodide and leads to a defect in thyroid hormone biosynthesis. The number of cases reported with this defect is 22,²⁻²¹ including total or partial defects.

Treatment of these patients has not been definitively established.¹,¹⁹ High doses of iodide have been recommended to increase the plasma/thyroid gradient of inorganic iodine and consequently raise the iodide intra-thyroidal concentration by simple diffusion.⁵,⁶ This would permit thyroid hormone synthesis in a normal way. Long term treatment doses, along with possible side effects on thyroid size and function are not exactly known. On the other hand, iodide itself has been involved in potentially beneficial effects.¹⁵ Two siblings with congenital hypothyroidism due to total failure to transport iodide are reported here. Their initial evaluation was done in 1973, followed up by twelve and a half years of treatment with high doses of oral potassium iodide (KI).

Material and methods

Patients

Patient A was a 15 year old boy with goitre at the beginning of the study in 1973. His mother and maternal aunt had normofunctional goitre, and a sister (patient B) had congenital hypothyroidism; two other brothers were in good health. His parents were not consanguineous. His goitre had been observed as a baby and was treated with thyroid extracts until one month before being studied. Due to psycho-motor delay, he had been put in a centre for the mentally retarded. His voice was deep and his reasoning was slow with tardy responses. His skin was dry and rough and his pulse rate 65/min. As shown in Table 1, he had a 40 g soft goitre, undetectable total serum thyroxine (T₄), high serum thyroid stimulating hormone (TSH), almost unnoticeable ¹³¹I uptake at all times studied, with normal urinary iodine excretion during 24 hours. The ¹³¹I salivary/plasma (S/P) ratio was 1. All these data fulfill the diagnostic criteria for complete iodide transport defect. The psychointellectual study by the Raven test placed him in percentile 5.

In May, 1973, treatment with potassium iodide in an 18 mg/ml solution was started (containing 1 mg per drop). The initial iodine dose was 18 mg/day, and later variations were established depending on the clinical evolution and analytical evaluation of thyroid func-
tion, in order to reach euthyroidism. The goitre disappeared and his final height was 164.5 cm.

Patient B was a 9 year old girl, sister of the patient A, diagnosed of congenital hypothyroidism at the moment of birth. She had been treated with thyroid extracts until one week before the study. She had no goitre and was only slightly mentally retarded. Total T₄ was in the normal range and TSH was slightly elevated, 5.2 μU/ml. Thyroid ¹³¹I uptake was 1% and there was no change after exogenous TSH stimulation; 24 h urinary iodine excretion was normal. The salivary/plasma radioiodide ratio was 0.96. These findings confirmed the same diagnosis as her brother's (see Table 1). After the study, she was treated with 18 mg/day iodine, the dose later varying depending on clinical evolution to reach normal clinical and analytical thyroid function. Menarche occurred at 12 years and her final height was 156 cm. In September 1985 she became pregnant and iodide was therefore discontinued, replaced by T₄. Her daughter has neither hypothyroidism nor goitre.

The mother of patients A and B was also studied, because of goitre, but the ¹³¹I uptake by the thyroid was normal and the salivary/plasma (S/P) radioiodide ratio was normal, 36.9, and she had normal serum thyroid hormone and TSH.

Methods

A TRH test was done giving 400 μg synthetic TRH (PREM, Barcelona) in an intravenous bolus after an overnight fast. Total serum T₄, triiodothyronine (T₃) and free T₄ were measured by RIA (Diagnostic Procedure Corporation) and TSH, growth hormone and prolactin were determined by standard commercial RIA (Sorin). S/P radioiodide ratio was calculated by measuring the radioactivity of saliva and serum aliquots collected after 50 μCi ¹³¹I oral administration. Protein-bound ¹³¹I was calculated by radioactive counting of the trichloroacetic acid precipitable material after 24 hours of the ¹³¹I trace dose. Total urinary iodine, plasma inorganic iodine (PII) or total serum iodine were measured according to the Benotti & Benotti method.

**Table 1** Clinical and analytical data of patients and mother at time of diagnosis

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>15</td>
<td>12</td>
<td>45</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.3</td>
<td>25.2</td>
<td>53.2</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.61</td>
<td>1.31</td>
<td>1.54</td>
</tr>
<tr>
<td>Goitre (g)</td>
<td>~40</td>
<td>no</td>
<td>~60</td>
</tr>
<tr>
<td>Total T₄ (μg/dl) (normal 5–11)</td>
<td>indetect.</td>
<td>5.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Serum TSH (μU/ml) (normal &lt;2.5)</td>
<td>68</td>
<td>5.2</td>
<td>1.9</td>
</tr>
<tr>
<td>24h ¹³¹I uptake (%) (normal 15–45)</td>
<td>1</td>
<td>1</td>
<td>57</td>
</tr>
<tr>
<td>Protein-bound ¹³¹I (%) (normal 0.02–0.2)</td>
<td>0.03</td>
<td>0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>Urinary iodine (μg/24h) (normal 50–200)</td>
<td>170</td>
<td>47.5</td>
<td>—</td>
</tr>
<tr>
<td>¹³¹I S/P ratio (normal &gt;10)</td>
<td>1.19</td>
<td>0.96</td>
<td>36.9</td>
</tr>
<tr>
<td>Plasma inorganic iodine (PII) (μg/dl) (normal 0.4–0.6)</td>
<td>—</td>
<td>0.09</td>
<td>—</td>
</tr>
<tr>
<td>¹³¹I thyroid/thigh (normal &gt;10)</td>
<td>—</td>
<td>1.15</td>
<td>—</td>
</tr>
<tr>
<td>24h urinary ¹³¹I (%) (normal 65–90)</td>
<td>—</td>
<td>85</td>
<td>—</td>
</tr>
<tr>
<td>Psychointellectual study (I.Q.) (Raven, PC) (normal 90–100)</td>
<td>5</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

S/P = salivary/plasma

Results

Figure 1 shows biochemical results during treatment with iodide of the two patients over twelve and a half years (A) and eleven and a half years (B), respectively. Dosages varied between 10.3 and 22 mg/day of iodine. Urinary iodine ranged between 9 and 17.1 mg/day, and serum total iodine varied between 100 and 210 μg/dl.

In both patients, T₄ and T₃ were in the normal range throughout the years of treatment, and, on a long term basis, there was a tendency for T₃ to change parallel to the amount of iodine given. When free T₄ was included in follow up treatment, it was in the normal range also. The TSH peak response to TRH was always in the normal range, and suppression never occurred, excluding hyperfunction at any therapeutic iodine dose.

Basal prolactin and its response to TRH, as well as basal growth hormone and cortisol and their response to exogenous hypoglycaemia, were normal during the treatment.
IODIDE TREATMENT IN THYROID TRANSPORT DEFECT

Patient A

Iodine (mg/day) 18 15 10 13

T₄ µg/dl

Year


Patient B

Iodine (mg/day) 18 15 21 22

T₄ µg/dl

Year


Figure 1  Iodine dose, total T₄ and T₃, free T₄ and TSH peak response to TRH during twelve and a half years (patient A) and eleven and a half years (patient B). •—•, T₄; ○—○, free T₄; Δ—Δ, T₃; □, TSH peak to TRH.

Discussion

In both siblings, the findings fulfil diagnostic criteria required to identify iodide transport defect: thyroid uptake very low or absent, not due to TSH defect or iodide contamination or exogenous thyroid hormone administration; iodide transport defect in saliva; and response to treatment with iodide. In untreated patients, the presence of differing degrees of goitre and hypothyroidism is usual. Patient B had no goitre, nor
hypothyroidism due to treatment with thyroid extracts from the time of birth until one week previous to the study. Other investigations and the later response to treatment excluded other causes of hypothyroidism.

Previously, only two families with siblings affected with this disorder have been described.\textsuperscript{11,16} The rareness of this case and its low frequency in families make the establishment of a genetic transmission pattern difficult. The consanguinity described in other cases\textsuperscript{\textsuperscript{2,11,13,16}} has been excluded in our patients.

There is only one reported case with long term follow-up iodide treatment, which only lasted one year.\textsuperscript{19} The efficiency of this treatment in another patient for 20 years has been reported without details.\textsuperscript{1}

In most other cases, after diagnosis, substitution therapy with thyroid hormones was carried out. This could be for practical reasons, because some authors consider iodide treatment to be more physiological.\textsuperscript{5,16}

In previous reports euthyroidism was brought about with iodide doses between 2.3 and 100 mg/day,\textsuperscript{16} or when total plasma iodide concentrations were 10 to 15 $\mu$g/dl.\textsuperscript{5,15} In only one case, the required dose was 63 mg/day, with a plasma iodine concentration of 33 $\mu$g/dl.\textsuperscript{9} Even with the widest range of iodide given to our patients, thyroid function was always normal, including at the lowest dose of 10.3 mg/day. The highest doses did not have any of the previously described side effects, such as goitre with hypofunction,\textsuperscript{22} hyperfunction\textsuperscript{22,29} or thyroiditis.\textsuperscript{24,29} It is suggested that long term high plasma inorganic iodine concentrations produce no inhibitory effects on the biosynthesis of thyroid hormones. On the other hand, other authors have reported that by sharply raising plasma inorganic iodine up to 3900 $\mu$g/dl, even for shorter periods of time\textsuperscript{19} such an effect was produced.

In agreement with others, in this study we have confirmed that hyperthyroidism does not occur with these long term high plasma iodide concentrations,\textsuperscript{15,16} although it has been found to occur in one case.\textsuperscript{4}

Experimentally, hypothyroid dogs treated with iodide had follicular necrosis with massive loss of thyroid hormones into plasma.\textsuperscript{24,29} Similar to other studies, no extra-thyroidal side effects were observed.\textsuperscript{30}

In conclusion, iodide treatment in patients with iodide transport defect achieves normal thyroid function on a long term follow-up with no side effects.

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References


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