Association of Iodine Organification Defect and Ectopy of the Thyroid Gland in a Patient with Primary Congenital Hypothyroidism

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We describe a neonate with primary congenital hypothyroidism due to an ectopic thyroid gland associated with a positive perchlorate discharge test suggestive of a partial iodine organification defect. To our knowledge, such an association has not been described previously. The implication of such an association is discussed.

Neonatal screening programmes for congenital hypothyroidism (CH) have revealed an incidence of approximately one in 2500-4500.\(^1\)\(^2\) Primary congenital hypothyroidism can be due to an absent or hypoplastic gland in 35\% of cases, an ectopic gland in 43\% or an inborn error of thyroid hormone metabolism in 22\%.\(^3\) Determination of the cause of CH has genetic, epidemiologic and prognostic importance.\(^4\)

We present a case of primary CH with an ectopic thyroid gland which was associated with abnormal perchlorate discharge test suggesting partial iodine organification defect. To our knowledge, this is the first child reported in the English literature with this combination documented by \(^125\)I thyroid uptake and scintigraphy, and perchlorate discharge test.

Case Report
This infant boy is the third child of a 26-year-old Yemeni mother. The parents were not consanguineous and had no history of thyroid dysfunction. The pregnancy had been normal. The mother had not received any medication containing iodine or an antithyroid agent. The mother did not have goitre or signs of hyperthyroidism or hypothyroidism. The boy was born at term by spontaneous vaginal delivery. At birth the infant weighed 4250 g and was 55 cm long. The hospital course was complicated by mild neonatal jaundice which was due to ABO incompatibility and he was discharged at 5 days of age. An abnormal cord screening test, detected as a result of a pilot screening study at Ministry of Health hospitals in Riyadh led to the infant being recalled at 7 days of age. The cord screening test revealed: thyroid stimulating hormone (TSH) 460 mIU/l (normal range for age, 2-40 mIU/l) and thyroxine (T\(_4\)) 54 nmol/l (normal range for age, 85-225 nmol/l). He was noted to have jaundice, large posterior and anterior fontanelles, but he had no goitre. Thyroid function showed (T\(_4\)), 1.1 nmol/l (normal range for age, 1.2-4.0 nmol/l), T\(_4\), 40 nmol/l (normal range for age, 110-285 nmol/l), TSH 560 mIU/l (normal range for age, 2-18 mIU/l), thyroid microsomal antibodies (TMA) test was negative, serum thyroglobulin (Tg) 45 \(\mu\)g/l (normal range for age, <50 \(\mu\)g/l) and serum thyroxine binding globulin (TBG) 26 mg/dl (normal range for age, 12-28 mg/dl). The epiphyses of the distal femora and proximal tibia were visible on a radiograph. As Technetium 99m pertechnetate (Tc\(^{99m}\)) scan showed
Figure 1. Technetium 99m thyroid scan demonstrating a sublingual gland

Table 1
Thyroid function tests in parents and siblings of the patient

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>TSH mU/l (normal 65-160 adults, 1.8-3 adults, children)</th>
<th>T&lt;sub&gt;3&lt;/sub&gt; nmol/l</th>
<th>T&lt;sub&gt;4&lt;/sub&gt; nmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>34</td>
<td>1.1</td>
<td>154</td>
<td>2.6</td>
</tr>
<tr>
<td>Mother</td>
<td>26</td>
<td>1.4</td>
<td>140</td>
<td>2.4</td>
</tr>
<tr>
<td>Sibling (1)</td>
<td>16</td>
<td>1.1</td>
<td>172</td>
<td>2.9</td>
</tr>
<tr>
<td>Sibling (2)</td>
<td>24</td>
<td>0.9</td>
<td>165</td>
<td>3.1</td>
</tr>
</tbody>
</table>

an enlarged gland in a sublingual location with a normal uptake (Fig. 1). Thyroid uptake and scintigram following 100 μCi of 123I was performed and showed a sublingual thyroid with high radioactive iodine uptake of 19% and 24% at 6 and 24 h respectively. Perchlorate discharge test was performed after oral administration of 100 μCi of radioactive iodine (123I) using a scintillation probe and scaler, 1 and 2 h thyroid uptake was determined followed by 0.5 g oral dose of potassium perchlorate. Thyroid uptake was subsequently measured every 15 min for 1 h and 30 min for an additional 1 h. Perchlorate discharge test revealed 32% discharge which indicates partial organification defect. Both parents and siblings were clinically and biochemically euthyroid and in particular there was no evidence of goitre (Table 1). On day 12, the baby was started on l-thyroxine 50 μg daily (11.5 μg/kg/day). At 33 days of age he was clinically and biochemically euthyroid, T<sub>3</sub> 2.7 nmol/l, T<sub>4</sub> 213.8 nmol/l, and TSH 6.6 mU/l (normal range for age, <10 mU/l).

At the time of writing this child was almost 11 months old. It would be interesting to repeat the perchlorate discharge test to see if the organification defect was transient. However, we believe that it would be unsafe to discontinue therapy for a period of 4-6 weeks in order to carry out this procedure as long as the patient is less than 3 years old. Such an interruption in therapy might affect brain growth. There are other methods of investigating the same problem, for example, by performing a 123I scan and perchlorate discharge test after TSH administration whilst the patient remains on therapy. Unfortunately, we do not have the facilities to carry out this test.
Discussion
The presence and location of thyroid tissue in a hypothyroid child has direct bearing on genetic counselling and prognosis. Athyreosis and thyroid ectopy recur very rarely in the same family, whereas hypothyroidism due to defects in thyroxine synthesis or release are inherited as autosomal recessive traits with an estimated frequency of 25% in siblings.6 The aetiology of the thyroid ectopy is unknown and it may be multifactorial.

The diagnosis of primary hypothyroidism was established in this infant on the basis of high TSH and low T₄ and T₃ values, while ectopy and organification defect were explained on the basis of Tc⁹⁹⁰¹ uptake, TSH uptake and scintigraphy, and perchlorate discharge test. The finding of a normal level of serum thyroglobulin in this patient reflects the presence of a significant amount of functioning thyroid tissue.6,7 We did not examine urinary iodine excretion in our patient, and the mother received iodine at the recommended daily allowance during pregnancy. It is thus unlikely that this infant was iodine deficient in fetal life. Since serum thyroid antibodies were not detected in the infant it is equally unlikely that his hypothyroidism was caused by thyroiditis. The finding of ectopic thyroid tissue and increased perchlorate discharge, which suggest partial iodine organification defect, is of interest. In reviewing the literature on the subject, no similar association has been described. Whether these findings of increased Tc⁹⁹⁰¹ uptake and perchlorate discharge represent a true partial organification defect or a transient state secondary to immaturity of the organification enzyme as postulated by De lange et al.8 and Nose et al.9 is worth mentioning and has its implication. True organification defect is an autosomal recessive disorder with a 25% likelihood of occurrence in siblings.5,10 On the other hand, transient organification defect if confirmed in this case and other cases, might indicate that some degree of delay in the development of synthetic mechanisms occur in the dysgenetic glands. In our case it is difficult to prove at this time as it is not justified to delay or stop therapy in children with hypothyroidism, in particular during early childhood, since thyroid hormones are known to play an essential role in the development and growth of the brain,4 and findings of normal thyroid functions with no clinical evidence of goitre in parents and siblings would not confirm the nature of this association. Finally, endocrinologists and paediatricians taking care of patients with congenital hypothyroidism should consider such a case which might contribute to our understanding of the pathogenesis of congenital hypothyroidism.

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References