Congenital hypothyroidism detected by neonatal screening: relationship between biochemical severity and early clinical features

D B Grant, I Smith, P W Fuggle, S Tokar, J Chapple

Abstract

The relationships between biochemical severity of hypothyroidism (as judged by plasma thyroxine) and the clinical and radiographic findings at diagnosis were evaluated in 449 infants born in 1982–4 with congenital hypothyroidism identified by neonatal screening. Details of pregnancy, delivery, and the neonatal period were also examined and compared with the findings in a normal population of 36 727 infants born in 1988. Infants with plasma thyroxine values of 30 nmol/l or less had a significantly higher incidence of prolonged jaundice, feeding difficulties, lethargy, and major malformations. More severe delay of bone maturation on a knee radiograph, and a higher proportion of thyroid agenesis on isotope scan. In contrast, an ectopic or hypoplastic gland was more common in infants with plasma thyroxine values above 30 nmol/l. Prevalence of illness in pregnancy and mode of delivery was not related to severity of hypothyroidism and were similar to figures for the normal population. Induction of labour, gestation over 40 weeks, and birth weight above 3500 g were significantly more common in the hypothyroid infants. Perinatal illness and congenital malformations were more common in the infants with low plasma thyroxine values at diagnosis.

Screening for congenital hypothyroidism started in the UK on a pilot basis in 1978; by mid-1982, after a recommendation by the Department of Health, routine screening had been introduced throughout the country. The Medical Research Council (MRC) Register of Children with Congenital Hypothyroidism was set up to collect detailed information on the outcome in children born with congenital hypothyroidism during 1982–4. Information on incidence, deaths, congenital malformations, and ethnic background has already been published. It has now become clear that there is considerable variation in the biochemical severity of hypothyroidism in children detected by screening and that this variation is closely related to the type of thyroid disorder which is present. In general, agenesis of the thyroid is associated with severe hypothyroidism, while ectopia, hypoplasia, or inherited defects of thyroid hormone synthesis are often associated with a less severe biochemical disturbance. The present paper examines the relationship between biochemical severity (as judged by plasma thyroid hormone concentrations at diagnosis) and clinical features at diagnosis, early biochemical findings (radiograph of the knee and isotope scan of the neck), pregnancy and perinatal events, and family history of thyroid disorder.

Subjects and methods

At the beginning of 1990 the register held the names of 472 children born between 1982 and 1984 who had been diagnosed by neonatal screening. This number includes 14 children who have since died and 15 who have been lost to follow up because of emigration or other change of address. Excluded from the present study were 23 children (including one who died) in whom plasma thyroid hormone concentrations had not been measured before treatment, leaving 449 children (139 boys and 310 girls).

DATA COLLECTION AND STATISTICAL ANALYSES

The paediatricians responsible for each child’s clinical management were asked to provide details concerning pregnancy and birth, diagnosis, initiation of treatment, physical health, and family background. This information was recorded using a standard proforma which included a checklist of symptoms at the time of first clinical assessment (usually after a positive screening report) and requested the results of diagnostic tests, and of a radiograph of the knee and isotope scan of the neck (if performed).

Thyroid hormone concentrations at diagnosis had been measured either as total thyroxine (T₄) (n=372), free thyroxine (FT₄) (n=75) or triiodothyronine (T₃) (n=2). Before the start of treatment, 68 blood specimens were obtained from 58 children, each specimen was analysed for total thyroxine and free thyroxine, and from this analysis an equation was formulated:

\[ \log T₄ = 2\cdot219 + 0\cdot9573 \times \log FT₄ \]

Using this equation (S Tillotson, et al, personal communication), 55 definitive results for plasma free thyroxine were converted to total thyroxine values. The distribution of initial thyroxine values for 420 children are shown in the figure.

To examine the relationship between severity of hypothyroidism and other clinical variables it was decided to divide the children into two groups, group I with thyroxine values of 30 nmol/l or less and group II with values greater than 30 nmol/l. The value of 30 nmol/l was chosen as it divided the subjects into two roughly equal groups. A further seven children...
with thyroxine results reported as 'less than 25 nmol/l' or 'less than 30 nmol/l' and 20 with free thyroxine values reported as 'less than 2-5 nmol/l' were ascribed to group I, with two who had plasma triiodothyronine values of 0-5 and 0-7 nmol/l, bringing group I to 215 cases and group II 234 cases.

The relationships between biochemical severity and other factors were explored in a series of tables. As not all of the subjects had a complete range of observations the tables are based on different combinations of subjects. Data on initial symptoms are available for 447 subjects, radiographs of the knee and isotope scans of the neck were carried out in 260 and 179 subjects respectively. Details of antenatal progress were available in 449 subjects, whether or not induction was undertaken in 393, mode of delivery in 421, gestation length in 430, and birth weight in 418.

Prenatal and perinatal findings were compared with those in an unselected population of 36 727 infants born in the north west Thames region in 1988.

Where appropriate, differences between groups I and II, and between the overall group of children with congenital hypothyroidism and the normal population, were assessed using $\chi^2$ tests, taking a probability of less than 0-01 to indicate statistical significance.

Results

SYMPTOMS OF HYPOTHYROIDISM

The prevalence of symptoms (table 1), as defined by the checklist sent to paediatricians, was consistently greater in group I than in group II although the differences were only significant for the five most common symptoms. Jaundice for more than three weeks was the most commonly reported symptom, followed by feeding difficulty, lethargy, umbilical hernia, macroGLOSSIA, constipation, cold or mottled skin, and hypothermia. In group I 16% of the children had no symptoms compared with 33% in group II, whereas 13% of children in group I showed five or more symptoms compared with less than 2% in group II.

In 38 infants (25 group I; 13 group II) who had been suspected of having congenital hypothyroidism on clinical grounds before the screening result was known there was a significantly increased incidence of persistent jaundice (74%) and feeding difficulties (58%). Lethargy (37%), macroGLOSSIA (24%), umbilical hernia (21%), constipation (13%), or a cold mottled skin (13%) were no more common than in the group as a whole.

BONE AGE AND THYROIDSCAN

In 260 children who underwent radiography of one knee at diagnosis (table 2), both epiphyses were absent in 54% of group I compared with 15% in group II. By contrast, both epiphyses were visible in 56% of group II, compared with only 27% in group I, a highly significant difference.

Only 179 infants had an isotope scan (table 3) and of these 40% showed an absent thyroid gland. However, in group I the proportion was 73% compared with only 12% in group II, whereas 61% of group II had an ectopic gland compared with only 15% in group I. A normally sited gland (indicating a probable defect of thyroid hormone synthesis) was present with approximately equal frequency (12% and 17%) in both groups of children. Hypoplastic or hemihypothyroid glands were reported in 10 infants all of whom had relatively mild hypothyroidism.

PREGNANCY AND DELIVERY

Sixty nine out of 447 mothers (15%) were reported as having some complication or illness during pregnancy (table 4), a prevalence very...
similar to that in the general population of
the north west Thames region; 9% of mothers had
hypertension or toxaeemia, and 2% insulin
dependent or gestational diabetes mellitus; 4% had
a range of different illnesses. Some form of
medication (other than iron and vitamin
preparations) during pregnancy was taken by
15%, the most common being antibiotics (5%),
antihistamines (3%), antihypertensives (2%), or seda-
tives (1%); 19% reported smoking more than
cigarettes daily and 3% drank alcohol
regularly while pregnant. There were no differ-
ences between groups 1 and II.

Mean maternal age at delivery was 27.1 years
(n = 341), compared with 28.0 years in the
general population; mean paternal age was 30.3
years (n = 286). The mode of delivery was very
similar in groups 1 and II and in the general
population. However, labour was induced in
53% of group I and 35% of group II, compared
with 15% of the general population, a trend
which is highly significant.

PERINATAL HISTORY
Overall, 44% of the hypothyroid children had
birth weights above 3500 g as compared with
36% in the general population, a highly signifi-
cant difference. However, there was no signifi-
cant difference in birth weight distribution
between group I and group II.

Problems at or after birth were reported in 25
hypothyroid infants (table 5), 16 in group I (7%)
and nine in group II (4%). In 11 infants illness
was associated with prematurity and in nine of
them the birth weight was less than 2500 g.
Thirty-two children were recorded as having
genital anomalies (other than of the thyroid
gland) when first assessed. Follow up revealed
anomalies in another three patients, giving an
overall incidence of 8%. Twenty-six of these
infants were in group I and nine were in group
II (p < 0.01). Ten children in group I died
before the age of 2 years, compared with three in
group II.

FAMILY HISTORY OF THYROID DISEASE
By the end of 1989, 15 children (3%) (including
two pairs of twins) had a sibling with congenital
hypothyroidism. Of the four who had thyroid
scans, three (including one pair of twins) had
a normal or enlarged gland, indicating probable
dysmorphogenesis. As thyroid scans were car-
ried out on less than half the patients only 153
children with dysgenesis of the thyroid have
been identified. These children have a total of
214 siblings, only one of whom has congenital
hypothyroidism. Two girls with congenital
hypothyroidism are maternal cousins and an
isotope scan in one of them showed no evidence of
thyroid tissue.

Thyroid disease was reported in 13 mothers
(3%); five had goitres, three thyroglossal cysts,
two hypothyroidism, and three hyperthyroidism.

**Discussion**

One of the most striking features of congenital
hypothyroidism to have emerged since the
introduction of neonatal screening is a very wide
range in biochemical severity at the time of
diagnosis. 3 4 Screening has allowed early identi-
fication of children with mild as well as severe
forms of the disorder and this probably accounts
for the apparent increase in the incidence of
genital hypothyroidism noted when screening
first began, along with a considerable
decline in the frequency of ‘juvenile hypo-
thyroidism’ presenting during later childhood.

In the present study 46 subjects (10%) had
normal plasma thyroxine values at the time of
diagnosis, and while it remains possible that a
few of these children may still prove to have
normal thyroid function, most (89%) have been
shown to have raised values of thyroid stimu-
lating hormone either on treatment or after its
temporary withdrawal.

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### Table 3 Thyroid scan findings in the 179 cases of congenital hypothyroidism. Results are
number (%)

<table>
<thead>
<tr>
<th>Thyroid scan result</th>
<th>Group I (n=84)</th>
<th>Group II (n=95)</th>
<th>Total (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent thyroid gland</td>
<td>61 (73)</td>
<td>11 (12)</td>
<td>72 (40)</td>
</tr>
<tr>
<td>Normally sized gland</td>
<td>10 (12)</td>
<td>16 (17)</td>
<td>26 (15)</td>
</tr>
<tr>
<td>Ectopic gland</td>
<td>13 (15)</td>
<td>58 (61)</td>
<td>71 (40)</td>
</tr>
<tr>
<td>Hypoplastic gland or hemihyroid</td>
<td>0</td>
<td>10 (11)</td>
<td>10 (6)</td>
</tr>
</tbody>
</table>

Group I and group II had initial plasma thyroxine concentrations ≤30 nmol/l or >30 nmol/l respectively.

Significance of difference between groups: χ²=72.31; p<0.001.

### Table 4 Pregnancy and perinatal data in 449 children with congenital hypothyroidism
compared with the normal population in the region. Results are number (%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>Normal population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness in pregnancy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension-toxaemia</td>
<td>15/215</td>
<td>7/234</td>
<td>12/202 (12)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3/215</td>
<td>7/234</td>
<td>4/183 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>7/215</td>
<td>13/234</td>
<td>20/199 (10)</td>
</tr>
<tr>
<td>Other pregnancy factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>31/215</td>
<td>58/234</td>
<td>90/199 (46)</td>
</tr>
<tr>
<td>Smoking</td>
<td>33/184</td>
<td>56/199</td>
<td>90/199 (46)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>4/164</td>
<td>2/173</td>
<td>6/234 (2)</td>
</tr>
<tr>
<td>Induction of labour</td>
<td>102/194 (53)**</td>
<td>69/199† (36)</td>
<td>171/393 (44)</td>
</tr>
</tbody>
</table>

Mode of delivery: Several
| Normal                     | 145/203 (71) | 156/218 (71) | 290/374 (78) |
| Assisted                   | 21/203 (10)  | 26/218 (12)  | 47/374 (12)  |
| Breech                     | 4/203 (2)    | 4/218 (2)    | 8/374 (2)    |
| Cerebro spinal section     | 23/203 (11)  | 31/218 (15)  | 54/374 (15)  |
| Gestation:                 |             |             |               |
| Below 37 weeks             | 20/209 (10)  | 11/221 (5)   | 31/329 (10)  |
| Over 40 weeks              | 100/209 (48) | 94/221 (42)† | 194/329 (19) |
| Birth weight               |             |             |               |
| Below 2500 kg              | 20/203 (10)  | 14/215 (6)   | 34/373 (9)   |
| Above 3500 kg              | 86/203 (42)  | 100/215 (46) | 186/373 (49) |

Group I and group II had initial plasma thyroxine concentrations ≤30 nmol/l or >30 nmol/l respectively.

Significance of difference between groups: **p<0.001 and between all hypothyroid subjects and
normal population: †p<0.001.

### Table 5 Perinatal illness, congenital malformations, and deaths in 449 children with congenital hypothyroidism

<table>
<thead>
<tr>
<th>Group I (n=215)</th>
<th>Group II (n=234)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal illness</td>
<td></td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia/aspiration</td>
<td>4</td>
</tr>
<tr>
<td>Septicaemia/necrotizing enterocolitis</td>
<td>6</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>1</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>1</td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>26*</td>
</tr>
<tr>
<td>Deaths</td>
<td>10</td>
</tr>
</tbody>
</table>

Group I and group II had initial plasma thyroxine concentrations ≤30 nmol/l or >30 nmol/l respectively.

Significance of difference between groups: *p<0.01.
In the present study there was a close relationship between the biochemical severity of hypothyroidism and clinical symptoms. Infants with plasma thyroxine concentrations below 30 nmol/l were much more likely to show prolonged jaundice, feeding difficulties, lethargy, umbilical hernia, and macroGLOSSIA than those with a less appreciable reduction in thyroxine values. Others have shown that such symptoms can also be used to differentiate hypothyroid infants from those with false positive screening results. In an important study from Finland, VIRTANEN compared the clinical findings at the age of 6 days in 95 newborn infants with hypothyroidism and 450 infants with false positive screening test results.6 Jaundice, macroGLOSSia, and hypothyroid appearance, abdominal distension, umbilical hernia, and cold skin were very much more common in the hypothyroid group, as were prolonged gestation, high birth weight, an above-average head circumference, and a good Apgar score. In a smaller study, ROCHICCIOLI ET AL found that the presence of macroGLOSSia, umbilical hernia, hypothyroid appearance, cold mottled skin, and a wide posterior fontanelle could be used to separate hypothyroid infants from those with false positive screening tests. Nevertheless, it should be noted that in the present study 16% of the infants with severe hypothyroidism were symptom free at the time of detection.

As has been reported previously, 3-5 biochemical severity was closely related to bone age. There is also evidence suggesting that the degree of bone age retardation may be of prognostic value with respect to later intelligence. 10-13 A relationship between thyroid scan results and the early biochemical findings is well recognised.14-17 In the present study, the thyroid scan findings were more closely related to severity of hypothyroidism than any other factors. Of those who were scanned, 80% showed hypodensity of the gland and 85% of these had plasma thyroxine values of 30 nmol/l or less; 46% had an ectopic, hypoplastic, or hemihyroid and only 16% of these showed a comparable reduction in plasma thyroxine values, illustrating the close association between agenesis and severe biochemical disease. Estimates of the prevalence of agenesis of the thyroid in series from other countries have varied from 15% to 51% but some of this variation may be due to different sensitivities in the scanning technique. The scan results described above suggest a prevalence of thyroid hormone biosynthetic defects of 15% in the UK, similar to that found in France and Finland (13%).14 This is a little lower than reported from North America (20-22%)18 and higher than in Switzerland (6%).15 Although our study failed to identify any differences in maternal factors during pregnancy or in the mode of delivery between infants with congenital hypothyroidism and the general population, there was a striking increase in the frequency of induced labour and higher frequencies of postmaturity and infants with birth weights over 3500 g. The increased prevalence of postmaturity is a well recognised feature of congenital hypothyroidism, 16 17 although its significance with respect to the physiology of labour is still uncertain. A number of authors have also reported increased birth weight as a feature of congenital hypothyroidism.11 16 17

As reported previously, congenital hypothyroidism is associated with an increased prevalence of other congenital anomalies, and almost 8% of the present sample had major malformations, compared with an expected frequency of 2-3%. The data suggest that some teratogenic factor is operating during early pregnancy but our study failed to identify any such factor other than the hypothyroidism itself.

This paper forms a report for the steering committee for the Medical Research Council's register of children with congenital hypothyroidism. We thank all the paediatricians across the country who have responded to our questionnaires and provided the data which make up this report. The study was supported by a project from the Medical Research Council.

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