Confirming congenital hypothyroidism identified from neonatal screening

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SUMMARY
All patients identified in the neonatal screening programme for congenital hypothyroidism in Northern Ireland between 1983 and 1993 were reviewed. 131 infants were recalled because of TSH elevation of whom 85 proved to have true permanent congenital hypothyroidism, while 44 had transient TSH elevation and 2 cases died before the diagnosis could be confirmed. TSH elevation at presentation was milder in the transient group and these infants were more likely to be unwell and/or suffering from congenital malformation.

INTRODUCTION
Congenital hypothyroidism (CH) is a largely preventable cause of learning disability. In the United Kingdom, neonatal screening for this condition began in 1978 and by 1982 a national programme was established. Early results estimated the incidence at 1 in 3937 live births. However, follow-up shows that some infants have transient abnormalities of thyroid function tests which do not require lifelong treatment. This study was performed to ascertain the incidence of permanent CH and transient neonatal abnormalities of thyroid function within a Health Service Region from January 1983 to December 1993 and to compare the clinical differences at presentation between these two groups.

PATIENTS AND METHODS
All infants in Northern Ireland from 1st January 1983 to 31st December 1993 were screened for congenital hypothyroidism at a recommended age between 6 and 8 days. Only patients born before 1994 were included as this allowed sufficient follow up, if necessary off treatment, to confirm the initial diagnosis. The number of live births was determined from the report of the Registrar General. Screening was performed by thyroid stimulating hormone (TSH) measurements from blood spots using Schleicher and Schuell No. 2992 filter paper cards. TSH was measured over the reported period using reagents supplied by Pharmacia UK (1983-1986) and EG&G Wallac Delfia TM Neonatal hTSH for the remaining period. The intra and inter coefficient of variation was <12% within the working range (10-250 mU/l whole blood) of the assays.

A whole blood TSH concentration of ≥10-25 mu/l was considered borderline and a second screening sample requested. Infants with a whole blood TSH >25 mu/l or a persistent borderline result were recalled for clinical assessment and venous blood sampling. Patients were considered to have permanent hypothyroidism if the serum TSH became abnormal (≤5 mu/l) after infancy while on treatment (indicating poor compliance or a need for an increase in thyroxine dosage) or if serum TSH increased to ≥5 mu/l on withdrawing treatment after the second birthday.
Transient elevations in TSH were defined in the following three circumstances:-

1. a persistent mildly elevated whole blood TSH >10 μu/l on screening with a serum. TSH <5 μu/l at recall.
2. a serum TSH ≥5 μu/l at recall which returned to normal in infancy without treatment.
3. normal thyroid function tests (serum TSH <5 μu/l) over a 6 month period after withdrawal of treatment.

RESULTS

Table shows the number of live births and number of positive TSH tests per year with 131 cases referred during the 11-year period. Two patients with mildly abnormal thyroid function tests at birth died in early infancy and could not be classified. Both were born preterm and one had Downs Syndrome and congenital heart disease. There were no known patients with a late diagnosis missed on neonatal screening during this period.

The incidence of permanent CH from January 1983 to December 1993 inclusive was 28.7 per 10^5 live births or 1 in 3478 live births. The annual incidence as shown (figure) suggests that in 1991 and 1992 an unusually large number of babies with permanent CH were diagnosed. Of the 85 patients with permanent CH, the female to male ratio was 2.5:1. Two children were from the same family, 3 had congenital heart disease (1 of whom also had Downs Syndrome) and 2 were preterm. At first recall the mean serum free thyroxine was 6.5 pmol/l (median 4.4 pmol/l, range 0.4-23.3 pmol/l) and mean serum TSH 350 μu/l (median 267.5 μu/l, range 11.9-1490 μu/l).

The incidence of infants with abnormal screening tests but subsequently found to have transient abnormalities was 1 in 6720 live births. Of these patients, 30% had normal TSH concentrations of <5 μu/l at their first recall, 37% had mildly elevated serum TSH concentrations during infancy which returned to normal without treatment and 33% were started on thyroxine in infancy which could subsequently be withdrawn. All 12 infants with a raised blood test TSH on screening but normal serum TSH (<5 μu/l) at recall remained clinically and biochemically euthyroid at follow-up. Of the 32 patients with raised serum TSH (≥5 μu/l) at recall, the male to female ratio was 1:1. Five siblings from 2 families were identified and the mother of another infant had developed hypothyroidism 1 year earlier.

| Year | Total live births | Recalled | Unclassified | Transient Abnormality TSH at recall | Permanent CH |
|------|------------------|----------|--------------|-----------------------------------|--------------|
|      |                  |          |              | 5< μu/l | ≥5 μu/l |             |             |
| 1983 | 27,255           | 11       | 0            | 1      | 3      | 7            |
| 1984 | 27,693           | 10       | 0            | 4      | 1      | 5            |
| 1985 | 27,635           | 9        | 0            | 2      | 1      | 6            |
| 1986 | 28,152           | 9        | 0            | 0      | 2      | 7            |
| 1987 | 28,865           | 10       | 0            | 1      | 2      | 7            |
| 1988 | 27,767           | 8        | 0            | 0      | 3      | 5            |
| 1989 | 26,071           | 11       | 1            | 1      | 0      | 9            |
| 1990 | 26,499           | 13       | 0            | 0      | 5      | 8            |
| 1991 | 26,252           | 19       | 0            | 2      | 5      | 12           |
| 1992 | 25,572           | 15       | 0            | 0      | 4      | 11           |
| 1993 | 24,909           | 16       | 1            | 1      | 6      | 8            |
| 1983-1993 | 295,670 | 131      | 2            | 12     | 32     | 85           |

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Myelomeningocele was present in 6 infants, congenital heart disease in 4, Downs Syndrome in 2 and prematurity in 2. Within this group, the median serum free thyroxine at recall was 19.1 pmol/l (range <2-28.4 pmol/l) and median serum TSH was 14.5 mu/l (range <5->320 mu/l).

DISCUSSION

The estimated annual incidence of permanent CH from 1983-93 in Northern Ireland was 1:3478 live births, slightly higher than the incidence of the 1982-1984 survey for England, Wales and Northern Ireland, and 1979-1993 Scottish review. Female preponderance is found in all 3 studies. A small rise in the annual incidence of permanent CH was observed in this study, but numbers were small. 33.6% of patients recalled turned out eventually to have transient disease, slightly higher than the Scottish figure of 25%. The difference may be attributed to the lower screening TSH value used to recall patients in the present review. Approximately one third of this group had normal serum thyroid function tests at recall and remained clinically and biochemically euthyroid at follow-up. The remaining two-thirds of this group were more problematic because of persisting abnormalities of thyroid function at recall. In retrospect, a risk factor for transient TSH elevation was present in the majority of these patients from a history of maternal hypothyroidism or siblings with transient TSH elevation, possibly as a result of maternal TSH receptor-blocking antibodies. Downs Syndrome and use of iodine either as an antiseptic for myelomeningocele, prematurity or in radiological investigations of congenital heart disease. High incidence of congenital malformation associated with transient TSH elevation has been shown. In addition, compared to infants with permanent CH, this group had an equal male to female ratio and a significantly higher free thyroxine and lower serum TSH level at recall.

All neonates who are started on thyroxine for CH and maintain normal thyroid function tests on follow-up should have their diagnosis confirmed by withdrawing treatment after 2 years of age and following up thyroid function. As previously shown, this is particularly relevant for ill or pre-term infants with less severe abnormalities of thyroid function before thyroxine replacement.

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