

## PAPERS AND SHORT REPORTS

## Growth, development, and reassessment of hypothyroid infants diagnosed by screening

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### Abstract

Thirty-six neonates in whom hypothyroidism was diagnosed after thyroid stimulating hormone screening were reassessed at 1 year. All had grown satisfactorily and the mental development scores were normal in all except two. Treatment was withdrawn in 32 and persistent hypothyroidism was confirmed in 31 cases. Thyroid stimulating hormone concentrations were raised in one-third of cases before the withdrawal of treatment and this was associated with generally lower concentrations of serum thyroxine (T4) and smaller doses of L-thyroxine than in those cases with normal concentrations of thyroid stimulating hormone.

In treating congenital hypothyroidism, serum T4 concentrations should be monitored regularly and the dose of thyroxine adjusted to maintain serum T4 in the upper part of the reference range.

### Introduction

The widespread introduction of neonatal hypothyroid screening in many parts of Western Europe and North America has shown a higher incidence of congenital hypothyroidism (about one in 4000-4500)<sup>1</sup> than was suspected previously from retrospective studies (about one in 6500-7000).<sup>2,3</sup> One explanation for this discrepancy might lie in the inclusion of cases of transient hypothyroidism among those diagnosed by screening.<sup>4</sup> For this reason, and because some children have no symptoms at diagnosis, a brief period of treatment withdrawal after one year

is usually advised to confirm the diagnosis of hypothyroidism. We re-evaluated 36 cases at 1 year and report our findings.

### Patients and methods

Primary congenital hypothyroidism was diagnosed in 36 neonates screened for raised concentrations of thyroid stimulating hormone from September 1978 to September 1980. The programme covered the North-east and North-west Thames Health Regions and details of the screening procedures and of the results have already been published.<sup>5,6</sup> At the time of diagnosis, investigations included measurement of serum thyroxine (T4), thyroid stimulating hormone, triiodothyronine (T3), reverse triiodothyronine, thyroxine-binding globulin, and thyroglobulin; estimation of bone age at the left knee and foot; and, in most cases, a <sup>123</sup>I thyroid scan. Detailed results of these investigations are available elsewhere.<sup>5,7</sup> The mean age of starting treatment was 30.6 ± SD 8.6 days (range 17-57 days). In most cases, day-to-day care was supervised by local paediatricians.

The children were recalled for re-evaluation and developmental assessment at the age of 1 year. At the first visit, while still being treated with L-thyroxine, they were weighed, length and head circumference were measured, and a Griffiths developmental assessment performed. Bone age was estimated and blood taken for estimation of serum T4, thyroid stimulating hormone, T3, reverse T3, thyroxine-binding globulin and thyroglobulin. A "T3 withdrawal test" was then performed as follows: triiodothyronine (10 µg twice daily) was substituted for thyroxine for three weeks then treatment was stopped completely for one week and a further blood sample taken. Thyroxine was restarted while awaiting test results. The purpose of the T3 withdrawal test was to use the short half life of triiodothyronine (two days) to minimise the period of treatment withdrawal.

### Results

Thirty-six infants (11 boys and 25 girls) were seen for developmental assessment. Their mean ages were 1.06 ± 0.07 years for the boys and 1.03 ± 0.06 years for the girls. Formal T3 withdrawal tests were performed on 32; parental consent was refused in one case who was athyrotic on the scan, three others had clinical or biochemical evidence of persistent hypothyroidism (a low T4 and high thyroid stimulating hormone) at the time of the first visit. Nine other cases who had been diagnosed during the first two years of screening were not seen; two had been lost to follow-up, two were unable to attend, and in five cases the local paediatricians felt that reassessment was unnecessary. All cases with mild hypothyroidism at initial diagnosis were reassessed.

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Table I gives growth data. The mean heights and weights were just above the 50th centile for the boys and just below the 50th centile for the girls at the mean age of assessment. None had heights or weights below the 3rd centile for age. The mean head circumferences, however, were larger than expected. The mean bone age at the wrist was  $1.02 \pm 0.28$  years.<sup>8</sup> Thus physical growth was generally satisfactory. One child showed a pattern of accelerating growth and was recognised as having cerebral gigantism from the facial features, growth pattern, advanced bone age, and characteristic findings on CT scan.<sup>9</sup>

TABLE I—Growth data at time of reassessment (36 cases). Results are means  $\pm$  SD

	Weight (kg)	Height (cm)	Head circumference (cm)	Age (years)
Boys (n = 11)	10.75 $\pm$ 1.31	77.6 $\pm$ 3.0	49.0 $\pm$ 1.7	1.06 $\pm$ 0.07
Centile	50-75	50-75	90-97	
Girls (n = 25)	9.57 $\pm$ 1.0	73.4 $\pm$ 2.9	46.8 $\pm$ 1.6	1.03 $\pm$ 0.06
Centile	25-50	25-50	75-90	

The mean quotient of results of the Griffiths assessment was  $104.2 \pm 7.9$ . Two children had Griffiths scores of less than 90; one was the child with cerebral gigantism and athyrotic hypothyroidism already mentioned (quotient 89) and the other a child who was undertreated at the time (quotient 81). There was no significant difference between the Griffiths quotients of the athyrotic cases and those with some thyroid tissue present on the initial scan. The mean scores for the subscales were as follows: scale A (locomotor)  $106.8 \pm 11.9$ ; B (personal/social)  $101.3 \pm 6.9$ ; C (hearing and speech)  $100.9 \pm 10.1$ ; D (eye/hand)  $105.0 \pm 8.8$ ; E (performance)  $104.6 \pm 12.2$ . The differences between subscales were not significant.

Table II gives the results of thyroid function tests before and after treatment withdrawal. Eleven (32%) of the children had raised serum

TABLE II—Results of thyroid function tests before and after withdrawal of treatment (32 cases). Results are means  $\pm$  SD (ranges in parentheses)

	Before	After	% Change
Thyroid stimulating hormone (mU/l) ..	11.0 (1- >40)	95 (5.2-340)	+870
T4 (nmol/l) .. .. .	130 $\pm$ 41 (72-277)	35 $\pm$ 29 (4-84)	-72.9
T3 (nmol/l) .. .. .	3.2 $\pm$ 0.6 (1.9-5.0)	1.4 $\pm$ 1.0 (0.5-3.2)	-54.4
Reverse T3 (nmol/l) .. .. .	0.4 $\pm$ 0.1 (0.2-0.5)	0.1 $\pm$ 0.2 (0-0.7)	-66.6
Thyroxine-binding globulin (mg/l) ..	14.6 $\pm$ 3.5 (8.0-20.9)	15.1 $\pm$ 4.6 (6.9-20.1)	+3

Conversion: SI to traditional units—T4: 1 nmol/l  $\approx$  0.07  $\mu$ g/100 ml. T3: 1 nmol/l  $\approx$  0.65 ng/ml.

concentrations of thyroid stimulating hormone (>10 mU/l) before treatment withdrawal, though only three of these had T4 values below 90 nmol/l (6.9  $\mu$ g/100 ml). The mean T4 value for these children was lower, however (mean  $100.9 \pm 20$  nmol/l (7.8  $\pm$  1.5  $\mu$ g/100 ml)) than that for children without persistently raised concentrations of thyroid stimulating hormone (mean  $144 \pm 40.8$  nmol/l (11.2  $\pm$  3.2  $\mu$ g/100 ml);  $t=4.01$ ,  $p>0.001$ ). In addition, the mean dose of thyroxine was lower in the children with persistently raised concentrations of thyroid stimulating hormone (mean  $35.2 \pm 12.2$   $\mu$ g/day) than in the others (mean  $53.8 \pm 15$   $\mu$ g/day;  $t=3.77$ ,  $p>0.001$ ).

After withdrawal of treatment none of the children had symptoms of hypothyroidism but T4 values fell in all 32 children tested while thyroid stimulating hormone values rose substantially in all but two. One of these two subsequently had treatment permanently withdrawn and has remained euthyroid. In this case transient hypothyroidism was suspected at presentation because of the absence of symptoms, a normal bone age, and a normal thyroid scan: results of the initial thyroid function tests had been only marginally abnormal (serum T4 60 nmol/l (4.7  $\mu$ g/100 ml), serum thyroid stimulating hormone 36 mU/l). The second case had a pronounced fall in T4 to 37 nmol/l (2.9  $\mu$ g/100 ml) but no rise in thyroid stimulating hormone. Later, treatment was stopped for six weeks: the concentration of thyroid stimulating hormone rose to 57 mU/l and the child has remained on

treatment. Serum T4 remained in the normal range after temporary withdrawal of treatment in one other child; he was known to have a mild familial organification defect with positive (30%) results of a potassium perchlorate discharge test. In all the other patients results of thyroid function tests were unequivocally abnormal after one week of treatment withdrawal.

## Discussion

Only two-thirds of the cases diagnosed by screening had evidence of intrauterine hypothyroidism, as judged by their retarded bone age, and one-quarter were asymptomatic. The discrepancy between the retrospective and screening incidences is probably accounted for by these cases with apparently "mild" hypothyroidism, who may make up a quarter to a third of the screened cases. We know from systematic thyroid scanning that most of these cases have either a large sublingual or normally sited thyroid gland.<sup>7,10</sup> The clinical course for patients with ectopic glands is for thyroid function to decline with age,<sup>10,11</sup> but some may remain sufficiently compensated through the thyroid stimulating hormone drive to be undetected in childhood. Those with normal thyroid scans have either transient hypothyroidism<sup>4</sup> or mild biosynthetic defects. Nevertheless, the above data suggest that transient cases are comparatively uncommon in the aetiology of mild hypothyroidism.

The high incidence of persistently raised concentrations of serum thyroid stimulating hormone was disturbing and may either indicate undertreatment or an alteration in the set point for suppression of thyroid stimulating hormone by thyroxine. Shultz *et al*<sup>12</sup> have suggested that this may be quite common in congenital hypothyroidism, as a result of hypothalamic-pituitary subresponsiveness or long-standing thyrotrophic hyperplasia, and that of thyroid stimulating hormone should not be used as the sole criterion of the adequacy of thyroid hormone treatment. As the T3 concentrations were normal in all these patients (except for one who was still clinically hypothyroid) and T3 is the most active thyroid hormone, possibly persistently raised concentrations of thyroid stimulating hormone may not be clinically important. On the other hand, in this study serum T4 concentrations and thyroxine doses were lower in these cases and they might have had normal thyroid stimulating hormone values if they had been given slightly larger doses of thyroxine. The recommendation that T4 concentrations should be kept in the upper half of the reference<sup>13</sup> seems reasonable, and a dose of 6-8  $\mu$ g/kg/day (50-75  $\mu$ g/day) at this age appears to be adequate.

Probably not every child diagnosed by neonatal screening need have a formal test of treatment withdrawal to confirm the diagnosis, as was performed in this pilot study. Though we had the advantage of knowing the aetiology of most cases from thyroid scans, such information is not always available and criteria for selecting cases which require further assessment after temporary withdrawal of treatment would be helpful. Such criteria might include: (a) infants who are asymptomatic, (b) infants with normal or near normal T4 values at diagnosis, and (c) infants with little or no retardation of bone age.

The satisfactory developmental progress of the infants is encouraging. The results of the New England screening programme<sup>14</sup> have also shown normal intellectual development at 3 or 4 years in all but a few children with gross clinical manifestations of hypothyroidism present at birth. The same study showed that undertreatment may prejudice intellectual development despite early diagnosis, thus emphasising the importance of using a dose of thyroxine appropriate for the child's age and weight and the need for regular biochemical monitoring of treatment, particularly during infancy.

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## Cardiac rhythm abnormalities in patients presenting with transient non-focal neurological symptoms: a diagnostic grey area?

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## Abstract

Eighty-nine patients attending neurology clinics with transient non-focal neurological symptoms were studied by routine electrocardiography and 24-hour monitoring of the electrocardiogram. In comparison with 109 control subjects there was no significant overall excess of arrhythmias (age-adjusted odds ratio 1.7,  $\chi^2=2.67$ ) except in the subgroup of patients under the age of 30 (odds ratio 11.6,  $p<0.05$ ). Bradyarrhythmias, but not tachyarrhythmias, were significantly more common in the patients (odds ratio 7.4,  $p<0.001$ ). Since patients can rarely be studied while they are having symptoms a working diagnosis must be based on a balance of probabilities: arrhythmias in young patients, or bradyarrhythmias in any patient, are likely to be clinically relevant. Ambulatory electrocardiographic monitoring contributed to the diagnosis in at least 25 of the patients. Nevertheless, the extent to which further investigations are pursued, and the form of treatment ultimately adopted, must also be influenced by the frequency and severity of the patients' symptoms.

## Introduction

The longstanding concept of an association between disturbance of cardiac rhythm and neurological symptoms was revitalised by the introduction of long-term ambulatory electrocardiographic monitoring,<sup>1,2</sup> particularly for patients with infrequent or sporadic symptoms. Most reports<sup>3-5</sup> of cardiac arrhythmias

detected by this method in patients with transient neurological symptoms have tended either to be anecdotal or to deal with more or less selected populations referred to a cardiac department. Clarke *et al*<sup>6</sup> cautioned against an uncritical acceptance of the clinical relevance of arrhythmias detected during asymptomatic periods. Nevertheless, there has been increasing demand for investigation in patients of this type, with important implications in terms of cost and the allocation of resources. We have therefore undertaken a case-control study of cardiac arrhythmias using ambulatory monitoring in consecutive patients with transient non-focal neurological symptoms presenting to a neurology service.

## Patients and methods

Eighty-nine patients were referred by their general practitioners over 30 months, and most were examined by NMH or CPW. Patients referred direct to the cardiology service were not included. All the patients had had transient episodes of loss or disturbance of consciousness (giddiness, dizziness, faintness) without focal neurological symptoms. Patients with a clear clinical diagnosis of epilepsy, transient ischaemic attacks, transient global amnesia, labyrinthine vertigo, or migraine were excluded. A total of 109 controls matched for sex and (roughly) for age were selected from outpatients, ambulant inpatients, and doctors, nurses, and physiotherapists. Fifty-seven controls had primary neurological disorders not known to be related to cardiac or cerebrovascular disease—for example, cerebral neoplasm, radiculopathy, and carpal tunnel syndrome; 35 had non-neurological diagnoses such as peptic ulcer, lymphoma, and skin disorders; and 17 were healthy.

Patients and controls were examined by DDEB and subjected to 12-lead electrocardiography (Elema Mingograph, three-channel), M-mode echocardiography (SKI Ekoline with Honeywell recorder), and at least one 24-hour period of ambulatory electrocardiographic monitoring (Oxford Instruments, Medilog system). All were encouraged to be up and about during the recording. A modified Marriott CM 1 electrode position was used. Tapes were analysed blind using either Oxford Instruments or Pathfinder equipment with visual monitoring. Some patients had repeat 24-hour recordings or intracardiac electrophysiological studies, or both, according to a standard protocol.<sup>7</sup>

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