Congenital hypothyroidism. Clinical and laboratory characteristics in infants detected by neonatal screening

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SUMMARY The clinical and laboratory characteristics of infants with neonatal hypothyroidism, and the age at which treatment was started are reviewed. The incidence of primary hypothyroidism was 1 in 3488 live births. Most of these cases were detected in a cord blood screening programme which was carried out between October 1973 and May 1980 in the Toronto region. Forty-eight infants with primary persistent hypothyroidism were classified by technetium scintiscanning as follows: 12 with athyrosis (non-visualised thyroid glands), 14 with ectopic thyroid glands, and 14 with goitrous thyroid glands. The remaining 8 infants comprised 4 with hypoplasia and 4 with transient hypothyroidism (2 idiopathic and 2 iodide induced). Although infants with athyrosis had a lower mean thyroxine value, their values overall were not significantly different from those of the other groups. Some infants, particularly those who were goitrous or ectopic, initially had normal thyroxine values. Skeletal maturation was more often delayed in athyrotic infants than in the ectopic or goitrous group. Radioactive iodine uptakes were appreciably higher in the goitrous group, and there was no significant difference between athyrotic and ectopic groups. The mean age at which treatment was started for all patients was 25 (range 6-120) days. The average age for starting treatment using initial thyroxine and secondary thyrotrophin testing in the initial stages of the cord blood screening was 36 days. The use of initial cord serum or dried blood thyrotrophin reduced the start of treatment to 14 days. It is concluded that: (1) It is important to determine the precise anatomical diagnosis, the biochemical severity, and the age at which treatment is started in order to assess the benefits of regional screening programmes in the detection of neonatal hypothyroidism. (2) Routine technetium scintiscanning before the start of treatment helps to determine the diagnosis. (3) Radioactive ^{131}I thyroid uptake studies are no longer routinely recommended; this is because of the radiation hazard and the lack of specificity in differentiating between the various anatomical types. (4) The feasibility of cord blood screening to detect the various causes of neonatal hypothyroidism is confirmed. (5) The time between final diagnosis and the institution of treatment can be reduced by 2 or 3 weeks if a thyrotrophin test is used initially from cord blood serum or, preferably, from dried blood spotted on filter paper; the latter is easier to post to a screening laboratory.

Screening programmes for congenital hypothyroidism have been conducted in North America since the early 1970s.¹ Preliminary results from Toronto,²⁻⁴ other centres in North America,⁵ Europe,⁶⁻⁸ and from Japan^{9 10} have been reported. The incidence of congenital hypothyroidism has been estimated to be between 1:3000 and 1:5000 live births.¹⁻⁸ Before the advent of thyroid screening it was felt that the majority of cases of congenital

hypothyroidism were due to athyrosis,^{11 12} but it is now apparent that there are other causes of primary hypothyroidism. As it is not known whether the anatomical diagnosis, the biochemical severity, or the age at which treatment is started affect the prognosis, these facts were recorded in each patient. It was hoped that a conclusion might be drawn on the benefits of a regional screening programme. In previous reports on infants with congenital

hypothyroidism detected by neonatal screening programmes, about half the patients were started on treatment without the underlying anatomical abnormality being defined.^{5 6 13 14} However at our centre each infant had been given his anatomical diagnosis before treatment was started. This has enabled us to determine more precisely the incidence of such abnormalities, and to characterise the clinical and laboratory features.

Methods

Each infant in this report was assessed at the time that neonatal hypothyroidism was detected and was then followed up at the Hospital for Sick Children, Toronto. Two methods of screening were used. Between October 1973 and December 1978 most infants were screened using an initial thyroxine (T4) screening test on cord blood and a supplementary thyrotrophin (TSH) on the lowest 10–15% of T4 results.^{3 4} Since January 1979 screening with an initial rapid TSH test¹⁵ from cord blood serum (recall 50 μ U/ml) or dried cord blood spotted on filter paper (recall >25 μ U/ml) has been used.¹⁶ A few infants who had been born outside metropolitan Toronto were detected by the Ontario screening programme which uses dried heel blood collected on filter paper at between age 3 and 5 days. In these infants heel blood was assayed initially for T4,¹⁷ and a secondary TSH screening test¹⁶ was performed on the lowest 10% of the blood T4 of each assay. Any infant with a TSH value >100 μ U/ml on cord blood serum, or >50 μ U/ml on dried heel or cord blood was admitted to the Hospital for Sick Children for immediate investigation and treatment. Any infant with a TSH value of 50 to 100 μ U/ml on cord blood serum, or 25 to 50 μ U/ml on dried heel or cord blood was recalled for a repeat serum sample and was investigated only if repeat values showed a persistent increase in TSH for his age.

They were assessed clinically by history and complete physical examination to detect predisposing factors such as maternal diet, drug ingestion, parental consanguinity, or family history of thyroid disease or signs of hypothyroidism. At recall all infants had serum taken for repeat T4, triiodothyronine (T3), T3 resin uptake, and TSH. After a blood sample had been collected an x-ray film of the knees was taken to estimate skeletal maturation.¹⁸ A low dose radioiodine uptake using 1 to 2 μ Ci of ¹³¹I was obtained at 0200 and 2400 hours, and a scan employing 0.5 and 2.0 μ Ci of technetium-99m with doses determined on the basis of surface area was performed to define the size, location, and activity of the thyroid gland except for any infant with an obvious diffuse goitre by palpation.

Classification. Athyrosis was diagnosed if no thyroid tissue could be seen by the technetium scan. An ectopic gland was diagnosed if thyroid tissue could be seen on scanning but was in an abnormal position. The ectopic group was classified still further as lingual if the position was at the base of the tongue, or as midline ectopic if the thyroid tissue was in the neck above the normal position of the thyroid gland. Goitrous glands showed an enlarged gland on scanning with increased uptake of technetium or, if performed, an abnormal ¹³¹I uptake. Any patient in whom scanning showed a thyroid gland in a normal position with or without diminished activity was placed in the miscellaneous group that comprised infants with possible hypoplasia or borderline normal-sized glands (who were treated with thyroxine when a persistent functional abnormality was observed on follow-up recall) or infants with normal-sized glands and evidence of improvement in thyroid function (transient hypothyroidism possibly due to either idiopathic¹⁹ or goitrogenic causes such as iodine^{3 4}).

Results

Anatomical types and incidence. Out of the 150 000 infants screened in the Toronto regional cord blood screening programme, 43 with primary hypothyroidism were detected. A further 5 infants were found in the Ontario programme, detected by heel blood. Twelve patients were found to be athyrotic, 14 had ectopic thyroid glands, 14 had goitrous glands, and the remaining 8 comprised the miscellaneous group (Table 1). The miscellaneous group comprised 4 patients with transient hypothyroidism and 4 with hypoplasia of the gland. Some patients had scintiscans indicating normally located thyroid glands with reduced size (hypoplasia) and as they may eventually be found to have only transient hypothyroidism once they have stopped their T4 therapy we shall confine ourselves to hypothyroid infants with athyrosis, ectopic, or goitrous causes.

In the ectopic group, 11 patients were observed to have a lingual thyroid. None of these was visible clinically. Three patients were found to have a midline ectopic gland. Two of these were visible in

Table 1 *Primary hypothyroidism—aeiological classification*

Types	Boys	Girls	Total
Athyrosis	2	10	12
Ectopic	5	9	14
Goitrous	3	11	14
Hypoplasia*	4	0	4
Transient*	1	3	4

*Hypoplasia and transient causes are classified as miscellaneous.

the neck. In the goitrous group, 9 of 10 patients who were scanned showed an enlarged gland with increased uptake of technetium. The one with a normal scan had clinical evidence of a goitre and an abnormal ^{131}I uptake.

Clinical studies. There were more girls in all groups (Table 1), but there were no differences in the gestational ages or birthweights. There was no family history of consanguinity or thyroid disorders in any baby found to have athyrosis or an ectopic thyroid gland. A history of consanguinity was obtained from 3 families whose infants were in the goitrous group. In 2 other infants in this group there was a family history of goitre of unknown aetiology. Congenital hypothyroidism was not suspected in any patient before recall. The symptoms and signs noted at the time of recall are shown in Table 2. A goitre was noted in one baby before recall but careful examination at recall showed goitres in 12 of the 14 babies in the goitrous group.

Laboratory studies. The results of tests on T4 and TSH in the screening programme and the results of

the tests at follow-up are shown in Tables 3, 4, and 5. As can be seen there was a wide range of values for T4. The mean values $\pm$ standard deviation were: athyrosis $4.86 \pm 1.62 \mu\text{g}/100 \text{ ml}$ ($62.55 \pm 20.85 \text{ nmol/l}$), ectopic $6.02 \pm 1.74 \mu\text{g}/100 \text{ ml}$ ($77.48 \pm 22.39 \text{ nmol/l}$), goitrous $5.76 \pm 1.75 \mu\text{g}/100 \text{ ml}$ ($74.13 \pm 22.52 \text{ nmol/l}$). These differences were not significant although the athyrotic group did have a lower mean value. In all three categories of congenital hypothyroidism the centile in a particular assay in which the T4 value was located showed great variability. In the athyrosis group, Case 3 was high at the lower 7.2 centile of the cord run whereas all others were below the 3rd centile. Three ectopic patients (Cases 13, 18, and 23) had values above the 3rd centile. Case 22, whose T4 was on the 27th centile, was detected fortuitously when a cord TSH was determined. In the goitrous group 4 out of the 9 infants had T4 values above the lower 3rd centile of the T4 assay run.

The T4 values at recall were lower than the cord serum result in all three groups (athyrosis $2.32 \pm 2.31 \mu\text{g}/100 \text{ ml}$ ($29.86 \pm 29.73 \text{ nmol/l}$); ectopic $4.33 \pm 2.48 \mu\text{g}/100 \text{ ml}$ ($55.73 \pm 31.92 \text{ nmol/l}$); goitrous $3.71 \pm 3.09 \mu\text{g}/100 \text{ ml}$ ($47.75 \pm 39.77 \text{ nmol/l}$). At this time the T4 result in the athyrotic group was significantly lower than in the ectopic group ($P < 0.01$) though not in the goitrous group. TSH values were greater than $100 \mu\text{U/ml}$ in every infant found to have athyrosis or an ectopic thyroid gland. Seven of the 14 patients in the goitrous group had TSH values greater than $100 \mu\text{U/ml}$. In 12 of these goitrous patients, the TSH value at recall was higher than it had been in the original screening test.

Skeletal maturation was delayed in 8 of 9 with athyrosis, in 6 of 11 infants with ectopy, and in 6 of 9 patients with goitres. Thus, in 7 of 30 infants with congenital hypothyroidism in whom bone age was

Table 2 Symptoms and signs of hypothyroidism (at the time of recall)

	Athyrosis (n = 12)	Ectopic (n = 14)	Goitrous (n = 14)
Hypoactivity/lethargy	3	1	0
Poor feeding	2	1	0
Constipation	2	0	1
Icterus > 2 days	7	5	0
Large posterior fontanelle	3	1	0
Oedema	1	0	2
Enlarged tongue	3	1	1
Hoarse cry	0	0	0
Dry skin	3	0	0
Umbilical hernia	8	3	0
Temperature < 36°C	0	1	0

Table 3 Thyroid function studies—athyrosis

Case	T4 (centile) in assay location	T4 (µg/100ml)		TSH (µU/ml)		Age at follow-up (days)
		Cord	Follow-up	Cord	Follow-up	
Toronto programme						
1	2.9	6.4	2.3	188	74	118
2	0.7	3.8	1.8	> 100	> 300	36
3	7.2	7.1	2.6	> 100	> 200	23
4	0.3	2.9	< 1.0	> 300	> 300	26
5	0.7	3.8	< 1.0	> 300	> 300	14
6	0.3	4.7	1.5	> 300	> 300	10
7†	2.3	6.4	2.4	> 300	> 300	8
8†	1.1	5.8	9.3	> 300	206	10
9†	—	2.8	< 1.0	> 100	> 300	21
Provincial programme						
10*	< 10	2.0	2.9	200	> 300	43
11*	< 10		1.1	100	> 300	30
12*	< 10	3.0	< 1.0	100	> 100	26

Conversion: traditional units to SI—T4 $1 \mu\text{g}/100 \text{ ml} \approx 12.87 \text{ nmol/l}$.

*Heel blood on day 3–5. †Primary TSH.

Table 4 Thyroid function studies—ectopic thyroid

Case	T4 (centile) in assay location	T4 (μg/100ml)		TSH (μU/ml)		Age at follow-up (days)
		Cord	Follow-up	Cord	Follow-up	
Toronto programme						
13	4.9	7.2	5.1	108	170	34
14	1.0	4.7	1.5	>300	>600	27
15	1.4	3.8	<1.0	>300	>300	15
16	0.6	4.5	2.5	>300	>300	14
17	1.6	6.5	4.8	>300	>300	14
18	3.4	7.9	6.0	172	153	23
19	1.0	7.6	11.0	145	395	15
20†	0.6	5.7	4.4	195	>300	9
21†	0.8	4.8	3.5	>300	>300	14
22†	0.7	4.7	3.3	>300	>300	7
23†	27.7	9.6	4.1	241	>300	12
24†	1.6	5.3	6.3	>300	279	9
25†	—	—	4.7	>100	>200	16
Provincial programme						
26*	<10	5.0	2.4	>100	>200	16

*Heel blood at day 3–5. †Primary TSH.

Table 5 Thyroid function studies—goitrous thyroid

Case	T4 (centile) in assay location	T4 (µg/100ml)		TSH (µU/ml)		Age at follow-up (days)
		Cord	Follow-up	Cord	Follow-up	
27	3.6	6.9	1.9	>192	>200	25
28	0.6	3.8	<1.0	>128	>400	22
29	0.4	3.7	3.1	>180	>160	31
30*	—	—	5.3	92	56	24
31	8.7	7.7	4.5	127	297	14
32	15.0	7.9	1.9	59	>300	26
33†	5.9	7.4	10.9	70	273	21
34*	—	2.8	5.3	38.5	>60	21
35	0.3	4.6	<1.0	215	>300	7
36	0.6	5.7	2.1	222	248	22
37†	0.3	4.1	3.4	87	271	14
38†	—	—	<1.0	>100	>200	6
39†	—	—	9.2	96	>100	7
Provincial programme						
40*	<10	7.5	1.4	35	250	28

*Heel blood at day 3–5. †Primary TSH.

assessed, skeletal maturation was normal; this observation has been noted previously.^{3,4}

The radioactive ¹³¹I uptake was significantly higher in the goitrous group at both 0200 and 2400 hours ($P < 0.001$, see Table 6). Although there was a difference in the mean values between the athyrotic and ectopic groups this was not significant. Eight of the athyrotic patients had normal uptakes at 0200 hours, but all were abnormally low at 2400 hours.

Table 6 Results of ¹³¹I uptake (mean $\pm$ SD)

	2 hours*	24 hours†
Athyrosis (n = 11)	5.43 $\pm$ 3.12	1.34 $\pm$ 1.06
Range	0–8.8	0–3.1
Ectopic (n = 12)	9.55 $\pm$ 6.09	5.86 $\pm$ 10.53
Range	4.2–25	0–38
Goitrous (n = 8)	39.41 $\pm$ 12.15	23.45 $\pm$ 11.18
Range	27.9–62	19.1–40

*Normal 3–9%. †Normal 9–26%.

Seven of the ectopic and 9 of the goitrous group had normal values at 2400 hours. One patient with an ectopic thyroid gland had a high ¹³¹I uptake at 0200 and 2400 hours. Clinically this baby had a large midline gland and may have had an enzyme disorder as well as an ectopic gland.

Age at start of treatment. Treatment with T4 was started at between 6 and 120 (mean 25) days. In Case 30 it started on day 91 and in Case 1 on day 120; both these patients were found early in the screening programme but the diagnosis and treatment had to be delayed for non-technical reasons. Between October 1973 and December 1978 the age at the start of treatment for 19 infants ranged from 12 to 120 (mean 36) days. Between January 1979 and May 1980 the age at the start of treatment for 16 infants ranged from 6 to 23 (mean 14) days, which is a significant decrease ($P < 0.025$).

Discussion

The incidence of primary hypothyroidism detected in the Toronto cord blood screening programme was 1:3488 live births. Twenty-five per cent of infants had athyrosis, 29% had ectopic glands, and 29% had goitrous glands. This is not in agreement with reports from other screening programmes.^{1 5 13 14} There may be several reasons for this difference. The population of Toronto comprises many ethnic groups; only 3 of the 14 babies with goitres were of Anglo Saxon ancestry. Most infants were detected by using cord blood whereas other large-scale programmes have used heel blood collected at between 3 and 5 days of age. Also, we used a higher cut-off point for a secondary TSH screening test on the lowest 10–15th centile of low T4 results from cord blood^{2–4} as well as the lowest 10th centile for heel blood,¹⁷ unlike other centres²⁰ which used a lower 2.5 centile of T4 results for TSH testing.²¹ A higher cut-off for secondary TSH testing of low T4 results is likely to detect more cases of ectopic or goitrous hypothyroidism²¹ since about 25% of infants with goitrous or lingual glands tend to have initial T4 results in the low to normal range.^{3 4 6} In many reported series, fewer than half of the patients detected were classified^{5 6 13 14} before treatment with T4 was started and many of them may have been either ectopic or goitrous.

As in other studies we found a greater number of girls.³ The reason for this preponderance is not clear. As could be expected clinical signs were more obvious in the athyrotic group, but even so not all patients had symptoms or signs of hypothyroidism. On recall, only 9 of 40 infants were found to have more than two of the clinical criteria proposed by Smith *et al.*²² to be indicative of hypothyroidism. Seven of these 9 patients were in the athyrotic group and the other two were in the ectopic group. Letarte *et al.*²³ designed a neonatal hypothyroid index in which various symptoms and signs were weighted according to the frequency that they found in their patients. When this index was applied to our patients only 7 of our 40 patients fulfilled their criteria, 6 of whom were in the athyrotic group and 1 was in the ectopic group. MacFaul and Grant²⁴ summarised the frequency of symptoms and signs seen within the first month in infants presenting clinically. If their results are compared with ours (Table 2) the incidence of abnormalities in our infants is lower except for the presence of an umbilical hernia and jaundice in the athyrotic group. It is apparent therefore, that although many infants with athyrosis will be detected within the first month of life on the basis of clinical history and examination, a great many cases will be missed, especially infants

with ectopic glands or goitres. In the goitrous group of patients a clinical goitre was present in most infants when they were examined by full extension of the neck.

The results of serum T4 on initial screening and follow-up showed a wide scatter, and all three groups overlapped. In several patients T4 values were normal. Fairly high initial T4 values have been reported in some athyrotic infants.²⁵ The precise reason for this is unknown. Non-visualised functioning remnants of thyroid tissue, transient increases in thyroxine binding globulin, or maternal blood contamination are possible factors. Every patient with athyrosis or an ectopic gland had TSH values greater than 100 μ U/ml, and although several patients in the goitrous group had TSH values lower than 100 μ U/ml, each of them had a goitre present on clinical examination. From these results and from our previous reports^{2–4} it can be concluded that primary TSH testing is a more sensitive screening test for primary hypothyroidism. This is in agreement with the findings of other North American,⁵ European,^{6 26 27} and Japanese^{9 10} centres.

Results of the ¹³¹I uptakes at both 0200 and 2400 hours overlapped greatly (Table 6). Although these results were of some help in the goitrous patients they did not differentiate between patients with athyrosis and those with an ectopic gland. Furthermore, the tests delayed the start of treatment and added an extra burden of radiation to the patients. In contrast, the technetium scan was very reliable in differentiating between the three groups of patients; it gave a rapid diagnosis, thereby enabling treatment with T4 to be started even before the repeat serum T4 and TSH values became available. Only in patients in whom a thyroid scintiscan was of normal location and size was it necessary to await the repeat serum results before beginning treatment to rule out transient hypothyroidism.¹⁹ We now no longer routinely perform radioactive ¹³¹I uptakes but instead rely on a technetium scan (or preferably a ¹²³I scan) to classify our patients.

Since January 1979 the age at which treatment began has been greatly reduced. This is partly because the screening system is now more efficient but it is also due to the use of primary TSH estimations in cord blood which was initiated in January 1979. The programme has shown the feasibility of detecting neonatal hypothyroidism from cord blood sampling. This study has also demonstrated that compared with initial T4 and supplementary TSH by either cord or heel blood screening programmes, the time between confirming the diagnosis and starting treatment can be reduced by 2 or 3 weeks if initial TSH testing is performed on cord serum or on blood spotted on filter paper.²⁸

It is clear that any patient detected should be classified by scintiscanning before starting treatment in order to evaluate the long-term benefits of a neonatal screening programme for the detection of congenital hypothyroidism and to determine the mental function attained by affected infants. It will then be important to relate the underlying anatomical lesion, the severity of thyroidal hypofunction, and the time that treatment was initiated and maintained, to the mental performance achieved by infants with congenital hypothyroidism. The benefits of detection and treatment of the various types of congenital hypothyroidism discovered by neonatal screening programmes can only then be truly assessed.

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