Contemporary Themes

Neonatal screening for congenital hypothyroidism by measurement of plasma thyroxine and thyroid stimulating hormone concentrations

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Abstract

Neonatal screening for congenital hypothyroidism was introduced in the City of Birmingham in 1980 by measuring concentrations of both thyroid stimulating hormone and thyroxine in plasma. Over two years 30 108 babies were tested. Thirty one babies were recalled because of thyroid stimulating hormone concentrations greater than 40 mU/l, of whom 12 were treated with replacement thyroxine. Six babies were found to have low thyroxine concentrations because of reduced thyroxine binding globulin and five raised thyroxine values because of increased thyroxine binding globulin.

As a result of this study screening was continued with measurement of thyroid stimulating hormone only as the primary test for congenital hypothyroidism, the thyroxine value being measured only when the concentration of thyroid stimulating hormone exceeded 20 mU/l.

Introduction

Congenital hypothyroidism may be detected biochemically in the newborn child when clinical evidence of the disease may be minimal or absent. Classically, a low concentration of thyroxine and an increased concentration of thyroid stimulating hormone occur in blood. The low thyroxine value is associated with an absent, ectopic, or hypoplastic thyroid gland and the high thyroid stimulating hormone concentration due to failure to switch off release by the anterior pituitary. If treatment is started early the clinical features can be prevented and the incidence of mental retardation considerably reduced.[1,2]

In most laboratories screening for congenital hypothyroidism has been incorporated into existing screening programmes for phenylketonuria using dried blood spots collected from infants during the first 14 days of life. Some centres have measured only thyroxine,[3] others only thyroid stimulating hormone,[4] while still others have measured both hormones, either in all specimens[5] or on a selective basis.[6-8] There are arguments in favour and against using either hormone as the preliminary screen (table I), and when setting up our pilot study in 1980 to detect congenital hypothyroidism in the neonatal period we decided to measure thyroxine and thyroid stimulating hormone in all samples for two years and then assess our data.

Most laboratories have used dried blood spots for screening for congenital hypothyroidism. We, however, were already using liquid blood for screening for phenylketonuria, and our assays for thyroxine and thyroid stimulating hormone were therefore established using plasma. We report our results of screening 30 108 babies over two years by measurement of both thyroxine and thyroid stimulating hormone concentrations in plasma from blood samples taken after six days of life.

TABLE I—*Advantages and disadvantages of using thyroxine or thyroid stimulating hormone as primary test for congenital hypothyroidism*

Assay	Advantages	Disadvantages
Thyroxine	Faster Cheaper Detects other thyroid abnormalities	Normal in some cases of congenital hypothyroidism Other causes of low thyroxine
Thyroid stimulating hormone	Always raised in congenital hypothyroidism Higher specificity Better sensitivity	Longer assay Larger sample volume More expensive Secondary and tertiary hypothyroidism missed

Materials and methods

Whole liquid blood samples were collected by capillary heel puncture using the system already used for screening for phenylketonuria and sickle cell haemoglobin.[9,10] An additional two capillary tubes (approximately 150 µl whole blood) were requested to allow duplicate measurement of both thyroxine and thyroid stimulating hormone in plasma.

Thyroxine radioimmunoassay—Thyroxine was measured by the method of Black *et al.*[11] Plasma (5 µl) was sampled directly from the glass capillary tubes and standards in the range 10-1000 nmol/l (0·8-78·0 µg/100 ml) and quality control samples added to barbitone buffer. 8-Anilino-naphthalene-sulphonic acid was added, to dissociate thyroxine from the thyroxine binding globulin, together with iodine-125 labelled thyroxine (Amersham International) and sheep antihuman thyroxine antiserum (Immunostics range, Seward Laboratories). The tubes were left at room temperature for three and a half hours and then at 4°C for a further 30 minutes. Polyethylene glycol and bovine γ globulin (Armour Pharmaceuticals) were added and, after mixing, centrifuged at 2300 rpm (800 *g*) for 30 minutes at 4°C. The supernatants were aspirated and the precipitates counted for ^{125}I. The concentration of thyroxine in each sample was determined in the usual manner for radioimmunoassay.

Thyroid stimulating hormone radioimmunoassay—An in house method was developed to measure thyroid stimulating hormone in 10 µl samples (N K Virdi *et al*, paper in preparation). Plasma, standards (1-64 mU/l), and quality control specimens were added to phosphate buffer containing bovine serum albumin (Miles Biochemicals). Rabbit antihuman thyroid stimulating hormone antiserum was added and left at room temperature overnight. ^{125}I labelled thyroid stimulating hormone was added, left for 24 hours at room temperature, and donkey antirabbit γ globulin in normal rabbit serum buffer (Wellcome Reagents) added. After 15 minutes at room temperature

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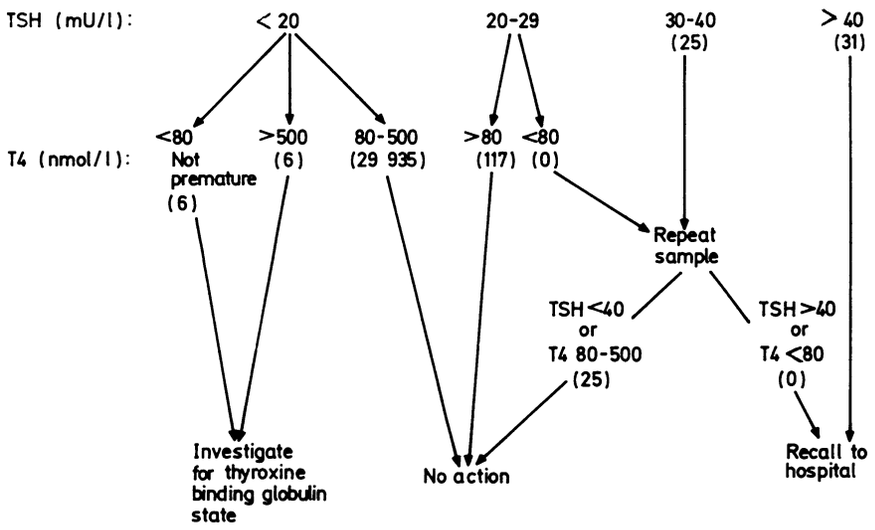
ammonium sulphate was added and the tubes centrifuged at 2300 rpm (800 *g*) at 4°C for at least one hour. The supernatants were aspirated, precipitates counted, and the thyroid stimulating hormone concentration determined.

Detection limits of assays—The limit of detection of the thyroxine assay was 20 nmol/l (1·6 μg/100 ml) and the within batch coefficients of variation 9·3% at 24 nmol (1·9 μg), 5·4% at 113 nmol (8·8 μg), and 4·2% at 157 nmol/l (12·2 μg/100 ml). The limit of detection of the thyroid stimulating hormone assay was 4 mU/l and the within batch coefficients of variation 4·5% at 9 mU and 3·1% at 25 mU/l. The between batch precision for thyroxine was 9·7% at 108 nmol/l (8·4 μg/100 ml) and for thyroid stimulating hormone 7·9% at 19 mU/l.

Follow up of patients—When repeat samples were required because of an insufficient sample or technical problems with the assay these were requested by telephone to the midwives via a central administration system. Repeat samples were usually received in the laboratory the next day. When a patient was recalled to the hospital the following procedure was adopted. The family's general practitioner was informed by telephone and permission sought for further follow up of the baby. The mother was requested to bring the baby to the screening laboratory at the Children's Hospital, and in most instances this occurred the morning after the first set of results had been obtained. A repeat sample of capillary heel prick blood was obtained for thyroxine and thyroid stimulating hormone measurements at the laboratory, and the baby had a full clinical examination.



Actions based on thyroid stimulating hormone (TSH) and thyroxine (T4) values in 30 108 babies tested over two years. (Numbers of children given in parentheses.)

Conversion: SI to traditional units—Thyroxine: 1 nmol/l≈0·08 μg/100 ml.

Results

During the initial period of the pilot study an unacceptably high number of repeat samples had to be requested, mainly because insufficient blood had been collected by the midwives. After an intensive education campaign, however, the number of repeat requests fell to an acceptable rate, which was maintained. Table II gives the reasons for the repeat samples requested during the second year of the study.

TABLE II—*Repeat samples requested from 15 707 babies screened over one year*

Reason	No	Percentage of total
Insufficient for thyroxine and thyroid stimulating hormone	114	0·73
Insufficient for thyroxine only	261	1·66
Borderline values of thyroid stimulating hormone or thyroxine or both	40	0·25
Total	415	2·64

PATIENT FOLLOW UP

The thyroid stimulating hormone result was used to categorise the babies initially as normal (<20 mU/l), borderline (20-40 mU/l), or abnormal (>40 mU/l) (figure). In the normal and borderline groups the thyroxine value was used to decide on the action.

NORMAL THYROID STIMULATING HORMONE VALUE

Babies whose plasma thyroid stimulating hormone concentration was <20 mU/l and thyroxine concentration was between 80 and 500 nmol/l (6·2 and 38·9 μg/100 ml) were considered normal. Two hundred babies (0·7%) with a normal thyroid stimulating hormone concentration had thyroxine values between 40 and 80 nmol/l (3·1 and 6·2 μg/100 ml); all were preterm, however, and no further action was taken. So far as we know none of these babies were subsequently diagnosed as having congenital hypothyroidism.

Six male infants who were not preterm had low thyroxine values with normal thyroid stimulating hormone concentrations. These babies and their mothers were recalled for biochemical and clinical follow up. Low concentrations of thyroxine binding globulin accounting for the reduced thyroxine value were found in all six babies (table III). One baby (case 5) had a very low thyroxine concentration (22 nmol/l; 1·7 μg/100 ml) in the initial screening sample. On recall, however, he was found to be clinically euthyroid and his thyroxine concentration was 69 nmol/l (5·4 μg/100 ml).

TABLE III—*Thyroxine and thyroxine binding globulin results in babies with abnormalities in thyroxine binding globulin*

Case No	Baby		Mother	
	Thyroxine (nmol/l)	Thyroxine binding globulin (mg/l)	Thyroxine (nmol/l)	Thyroxine binding globulin (mg/l)
	Decreased thyroxine binding globulin			
1	36	2·5	60	5·9
2	63	3·2	69	9·3
3	46	4·5	60	—
4	75	6·8	71	9·6
5	22	7·4	111	9·8
6	67	5·2	88	6·1
	Increased thyroxine binding globulin			
7	540	43·5	436	76·5
8	659	56·3	508	40·5
9	749	54·0	235	35·1
10	769	44·7	340	40·0
11	>1000	>50	348	31·1

Reference ranges—Thyroxine: adults 60-130 nmol/l (4·7-10·1 μg/100 ml). Thyroxine binding globulin: adults 6·0-16·0 mg/l; children aged 3-4 weeks 8·0-20·0 mg/l.
Conversion: SI to traditional units—Thyroxine: 1 nmol/l≈0·08 μg/100 ml.

His thyroxine binding globulin value was still low for his age. The five mothers of these babies in whom thyroxine binding globulin was measured had concentrations at the lower end of the reference range.

One baby with an initial thyroid stimulating hormone concentration of 15 mU/l and a thyroxine value of 57 nmol/l (4·4 μg/100 ml) was investigated for an abnormality in thyroxine binding globulin. The concentration was normal in both baby and mother, and as the baby was clinically euthyroid he was not followed up. At 8 months of age, however, his general practitioner referred him to the paediatrician for a goitre; his thyroxine concentration was found to be less than 20 nmol/l (1·6 μg/100 ml) and thyroid stimulating hormone value greater than 64 mU/l and thyroid replacement therapy was begun immediately.

Five male infants (cases 7-11) were recalled for similar investigations

because of a thyroxine concentration greater than 500 nmol/l (38·9 μg/100 ml) with a normal thyroid stimulating hormone concentration. In all these babies and their mothers the thyroxine binding globulin concentration was significantly increased to account for the raised thyroxine value (table III).

BORDERLINE THYROID STIMULATING HORMONE VALUE

In all babies with an equivocal thyroid stimulating hormone concentration (between 20 and 40 mU/l) the thyroxine value was greater than 80 nmol/l (6·2 μg/100 ml). As a precaution, however, those 25 babies with thyroid stimulating hormone values between 30 and 40 mU/l had repeat samples collected for both thyroid stimulating hormone and thyroxine measurements.

ABNORMAL THYROID STIMULATING HORMONE VALUE

Thirty one children were recalled to the hospital because of a high thyroid stimulating hormone concentration (greater than 40 mU/l). Of these, 12 were prescribed thyroxine replacement therapy (12·5 μg/kg body weight) either because of a low thyroxine value or because they had clinical symptoms of congenital hypothyroidism. Table IV summarises the thyroxine results in these babies with thyroid stimulating hormone concentrations greater than 40 mU/l. The initial and confirmatory thyroid hormone results in those babies treated, together with the age at which treatment was started, are shown in table V.

TABLE IV—*Thyroxine results in 31 babies with thyroid stimulating hormone greater than 40 mU/l. Figures are numbers of babies*

	Thyroxine (nmol/l)				
	<20	20-40	41-80	81-100	>100
Patients treated	1	5	4		2
Non-treated			2	3	13
Total*	1	5	6	3	15

*There was insufficient sample for thyroxine measurement in one baby.
Conversion: SI to traditional units—Thyroxine: 1 nmol/l≈0·08 μg/100 ml.

TABLE V—*Thyroxine and thyroid stimulating hormone results in 12 infants treated for congenital hypothyroidism*

Case No	Thyroxine (nmol/l)		Thyroid stimulating hormone (mU/l)		Age at start of treatment (days)
	Initial	Follow up	Initial	Follow up	
12	<22	20	>64	1400	11
13	140	75	46	>64	17
14	78	30	48	46	16
15	*	65	>64	>64	15
16	143	95	49	48	15
17	24	*	>64	*	12
18	67	26	>64	>128	64
19	*	48	>64	>128	39
20	40	35	>64	>128	11
21	39	31	>64	>128	75
22	<20	*	>64	*	20
23	39	26	>64	>64	13

*No result obtained.
Conversion: SI to traditional units—Thyroxine: 1 nmol/l≈0·08 μg/100 ml.

Against medical advice the mother of one patient (case 14) stopped giving thyroxine four weeks after treatment began, but the child's results returned to normal and remained so. One patient (case 19) was born with a tracheo-oesophageal fistula and subsequently developed renal failure and died. Another patient with this congenital abnormality (case 21) required surgery. Other than these cases the subsequent follow up of the treated group was uncomplicated.

The 19 other babies who were recalled were not treated. Although the thyroid stimulating hormone concentration was unequivocally raised on repeat testing, none of the babies had any clinical signs of congenital hypothyroidism. This group of babies were seen regularly for clinical examination and monitoring of their thyroxine and thyroid stimulating hormone concentrations. In two babies the high thyroid stimulating hormone value persisted with borderline thyroxine concentrations but these babies remained euthyroid.

Discussion

Screening of all neonates in the City of Birmingham for congenital hypothyroidism was introduced in 1980 at the Children's Hospital, using plasma to measure both thyroid stimulating hormone and thyroxine values. Initially collection of two extra capillary tubes of blood proved to be difficult and resulted in an unacceptably high number of requests for repeat samples. Nevertheless, after an intensive education programme for the midwives the number of repeat requests due to insufficient sampling fell to 2·4% of the total. Although we have been unable to find any published information about repeat sampling rates due to inadequate samples, information received by personal communication from other laboratories compares favourably with our experience. Our repeat rate of 0·25% (table II) due to borderline results was also comparable with those found in other studies.[12] The precision and sensitivity of our plasma thyroid stimulating hormone and thyroxine assay methods compare favourably with dried blood spot methods.[13-16] This enables our "screening" assays to be used for monitoring thyroxine replacement using small volumes of capillary blood, an important consideration in babies and young children.

A main problem when setting up a screening programme is to decide on the action limits. At the outset of our study the action limits we used were based on published data. To our knowledge no child with congenital hypothyroidism has been reported with an initial screening plasma thyroid stimulating hormone concentration of less than 20 mU/l; hence we decided to use this as our lower cut off value.

There were 200 premature low birthweight babies with thyroxine values of less than 80 but greater than 40 nmol/l (less than 6·2, greater than 3·1 μg/100 ml) who had normal thyroid stimulating hormone values and were not followed up. To our knowledge none of these babies went on to develop thyroid disease. This finding of lower thyroxine concentrations in premature babies has been reported by several workers.[17 18] Cuestas suggested that the low thyroxine value may be due to a lower concentration threshold for release of thyroid stimulating hormone in premature babies or, alternatively, that the thyroid gland in these babies may have a decreased ability to respond to thyroid stimulating hormone.[18]

None of the 11 babies found to have abnormalities in production of thyroxine binding globulin had any clinical symptoms and they were therefore not regularly followed up. All were boys, so supporting X linked inheritance of thyroxine binding globulin disorders.[19] In the five cases where thyroxine binding globulin was measured in the mothers of babies with low concentrations (table III) we found values either below or at the low end of the reference range. This variable activity found in the presumed heterozygous mothers has been reported by others.[19 20]

One baby with a thyroid stimulating hormone concentration less than 20 mU/l and an initial low thyroxine value was discharged as his thyroxine value on recall was normal, and at that stage he was clinically euthyroid. At the age of 8 months, however, he presented with typical biochemical and clinical signs of congenital hypothyroidism. We have no explanation for this. Possibly the hypothyroidism developed after birth in this patient, or this may have been a genuine "missed" case. The importance of not dismissing the possibility of hypothyroidism in older infants who had normal neonatal screening tests needs to be remembered.

All children with borderline thyroid stimulating hormone concentrations (20-40 mU/l) had normal thyroxine concentrations (>80 nmol/l; >6·2 μg/100 ml) and were not recalled, although those with values between 30 and 40 mU/l were retested. The ability to do thyroxine determinations in the same initial blood sample enabled us to take this step, which otherwise would have necessitated an additional 117 babies being retested. To our knowledge none of these children subsequently presented with thyroid disease.

Our recall rate due to raised thyroid stimulating hormone concentrations was similar to those found in other studies.[7 12 21] Of the 31 babies recalled, 12 began thyroxine replacement treatment. The decision to treat was based on the thyroxine concentration together with clinical assessment. We were not able to confirm the anatomical thyroid state by radioactive uptake scanning for thyroid tissue in any of the babies because of lack of local facilities.

In 10 of the 12 children treated (table V) the thyroxine value in the initial screening sample was less than 80 nmol/l and in all 12 the concentration had fallen when measured in the repeat sample taken just before beginning treatment.

Treatment was instituted in eight babies by 21 days of age (mean 14 days) and in one by day 28, but the remaining three were treated later (39, 64, and 75 days). These three babies were hospital inpatients and were tested late because of an inadequate system. This disturbing oversight was unacceptable not only for congenital hypothyroidism but also for screening for phenylketonuria. Since these events local efforts within the hospital to tighten up the procedure should ensure that all babies will be screened at 6-10 days of age in future.

The age before treatment began compared favourably with results from other centres. Hummer *et al* reported a mean age of 25·6 days (range 16-59) in 32 infants who required treatment[22]; Docheray *et al*, in 19 infants, reported a mean age of 15 days (range 10-29), one infant being treated at 10 weeks because of equivocal biochemical results[21]; and Mitchell *et al* reported a mean age of 25 days (range 6-120) at the start of treatment.[6] Nineteen babies who were recalled because of an initially raised thyroid stimulating hormone concentration (>40 mU/l) were not treated. In all cases the thyroxine concentration was greater than 80 nmol/l and they were clinically euthyroid. Thyroid stimulating hormone was monitored regularly in these babies, and in 17 cases values fell to normal at ages ranging from 2 weeks to several months. The two babies in whom the high thyroid stimulating hormone concentration persisted remained clinically euthyroid. These children, whose thyroid stimulating hormone concentrations returned to normal, and their mothers are currently being reviewed clinically and biochemically and the findings will be reported. Several other workers have reported cases of transient hypothyroidism. Delange *et al* found 11 cases among 5108 babies tested and the thyroid stimulating hormone in these reverted spontaneously to normal.[23] In three of these, however, massive iodine contamination was the cause and the other eight had serious perinatal conditions. Walfish *et al* in a report on 76 000 babies tested found four patients with a transient increase of thyroid stimulating hormone; two cases were believed to be a result of maternal iodine ingestion and two were of undetermined aetiology.[24]

Screening for congenital hypothyroidism by measuring both thyroid stimulating hormone and thyroxine concentrations in all samples has been a worthwhile study. Not only have children with congenital hypothyroidism been detected but children with transient hypothyroidism and abnormalities of thyroxine binding globulin production have also been found. Our incidence of congenital hypothyroidism (1:2520) was higher than reported by other screening centres. Nevertheless, because we have not had the opportunity of confirmatory thyroid scans and triiodothyronine withdrawal tests were not completed in all these babies the true incidence is still not known. One possible explanation of this high incidence may be related to our high Asian population; 23% of all babies tested are of Asian origin, whereas 42% of babies being treated are Asian.

By measuring the thyroxine concentration no case of primary pituitary hypothyroidism should be missed. We detected none in our study, which is not unexpected when the condition has a reported incidence of 6-10% of total neonatal hypothyroid cases.[5,25]

We have now stopped measuring thyroxine in all samples and restrict thyroxine measurement to those samples with a thyroid stimulating hormone value greater than 20 mU/l. Hence we now do roughly 200 such measurements a year. By selecting samples for thyroxine measurement in this way we can reduce the number of repeat samples required due to borderline thyroid stimulating hormone concentrations (20-40 mU/l) in the first sample, a factor of obvious importance to baby, mother, and midwife. The ability to measure thyroxine in the same initial blood sample has particular advantage for us in deciding which babies to treat, especially as we have no readily available scanning facilities.

After the completion of this two year study we have now decided that measurement of thyroid stimulating hormone is the preferred primary screening test for congenital hypothyroidism. Screening based on thyroxine values would have missed one baby with clinical evidence of congenital hypothyroidism whom we have treated. In addition, a significant number of babies with low thyroxine binding globulin concentrations (incidence in our study 1:5184) would be investigated unnecessarily. A possible disadvantage of screening using thyroid stimulating hormone is the detection of many babies with transiently raised values. Nevertheless, as we still do not know the long term importance of this finding we are continuing to follow up these babies. This study has enabled us to have confidence in our action limits for thyroid stimulating hormone.

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