Population screening for congenital hypothyroidism

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Summary and conclusions

A pilot screening programme for congenital hypothyroidism covering most of North London, Essex, Bedfordshire, and Hertfordshire entailed carrying out an assay of thyroid-stimulating hormone on single Guthrie dried blood spots. During one year 87 444 babies were screened and 26 cases of primary congenital hypothyroidism detected, giving an incidence of 1:3363. Only two cases (7·7%) had already been diagnosed on clinical grounds before the results of screening became available. In two other babies the diagnosis was delayed. The programme thus resulted in the early treatment of 22 babies, eight of whom already had pronounced features of hypothyroidism that had not been detected on routine clinical examinations.

Although definitive evidence will not be available for some years, the results suggest that the prognosis for most of these babies is likely to be improved by early diagnosis; thus the introduction of national screening should be delayed no longer.

Introduction

Neonatal screening for congenital hypothyroidism was first introduced in Quebec in 1974,[1] and since then several European countries including Switzerland,[2] Austria, and Denmark have introduced national programmes. This has been done because a considerable improvement is expected in the prognosis for intellectual development in children treated from very early in life. Although firm evidence for this is still not available, the preliminary results of developmental follow-up are extremely encouraging.[3] Screening for the disease by using a thyroid-stimulating hormone (TSH) assay on single dried blood spots (already available for Guthrie tests) was started at this hospital on a trial basis in May 1978, and systematic screening of most of the babies born in the North-east and North-west Thames Health Regions started on 1 September 1978. This report covers the one-year period up to 31 August 1979.

Methods

The project is closely integrated with an existing screening programme for phenylketonuria and uses the same staff for processing the Guthrie cards, punching the discs and placing them in the assay tubes, and arranging for repeat Guthrie specimens to be collected by health visitors. While insufficient blood spots were available routinely to perform the assay in duplicate, second spots were available in 45% of cases for reassay when required.

TSH ASSAY

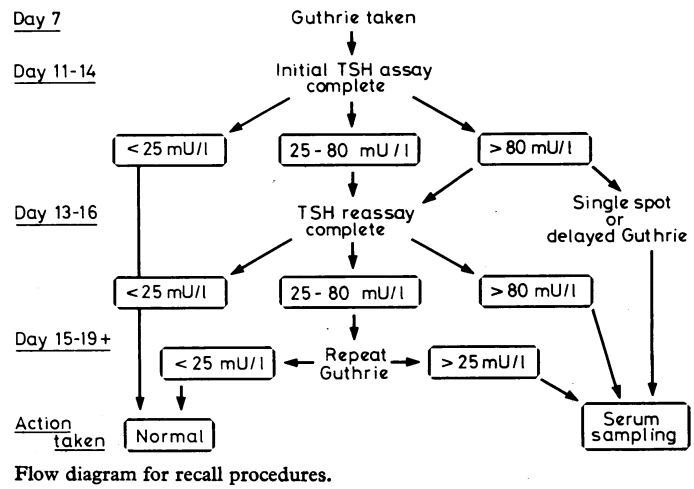
The TSH assay is based on the method of Rees *et al*[4] with a few minor modifications. Discs 6 mm in diameter are hand punched from the blood spots on Guthrie cards and placed in unmarked tubes in numbered trays holding 100 specimens. The tubes remain in the trays throughout the assay until finally counted in groups of 16 in a Nuclear Enterprises 1600 counter. The TSH radioimmunoassay uses a double-antibody technique and takes 48 hours. It is performed twice weekly, with batches of 800-900 per assay. Standards are prepared by using doubling dilution of human TSH (MRC 68/38) in normal human blood spotted on to Guthrie sheets over the range 0-640 mU/l. Each assay includes appropriate blanks, the standard curve in duplicate, and quality controls from patients with raised serum TSH concentrations. After counting, results are passed on line to a Hewlett Packard 9815S desk-top computer, which plots the standard curve, eliminates outliers, prints out high values, and performs various statistical analyses for quality control. Further details of the method and computer programme may be obtained from RWHE.[5]

The interassay coefficient of variation is between 20% and 32%, and comparison of several serum and blood-spot samples run in parallel showed a good correlation ($r=0{\cdot}97$, $n=25$). It takes 26 person-hours per week to perform the complete assay on about 1700 samples: 10 for processing the Guthrie cards and 16 for the laboratory work.

RECALL PROCEDURES

Arbitrary TSH values of 25 and 80 mU/l were chosen as cut-off points, except in a few assays with rather insensitive standard curves, when values up to 40 mU/l were chosen. The figure shows details of the recall procedures and appropriate timing.

TSH concentrations of 25 mU/l or less on the first or second assay of spots from the first Guthrie specimen were considered to exclude primary hypothyroidism. These negative results were not reported. When values between 25 and 80 mU/l were obtained in the first assay and confirmed on a second spot from the original Guthrie card a further blood-spot specimen was requested; if this yielded a TSH concentration over 25 mU/l a serum sample was obtained as



Flow diagram for recall procedures.

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rapidly as possible as the likelihood of congenital hypothyroidism was very high. A repeat Guthrie specimen was obtained for any value over 80 mU/l, even if the second spot TSH was normal. On several occasions babies were recalled for serum sampling on the basis of a single spot TSH over 80 mU/l to avoid delay in establishing a diagnosis.

DIAGNOSTIC CONFIRMATION

Babies in whom the screening tests yielded positive results were seen as outpatients to evaluate the severity of the hypothyroidism. In addition to a careful history and physical examination, serum thyroxine (T4), triiodothyronine (T3), and TSH concentrations and bone age were estimated and a ^{123}I thyroid scan done. The scan was omitted when a goitre was present. Iodine-123 was chosen for the low total body dose of irradiation.[6] The detailed results of these and other investigations in 16 cases of hypothyroidism are reported elsewhere.[7]

Results

NUMBERS OF BABIES SCREENED AND RECALLED

During the one-year period TSH was estimated on blood spots from 87 444 babies in 103 assays. In 87 212 cases the TSH concentration was below 25 mU/l in the first or second assay of spots on the initial Guthrie card and no further action was taken. In 182 babies a value between 25 and 80 mU/l was found on assay of the first spot, and a repeat Guthrie card was requested when the second assay confirmed the raised value or because a second spot was not available. With four exceptions the repeat Guthrie cards taken between 2 and 6 weeks of age all yielded TSH concentrations below 25 mU/l. Thus over the whole year the recall rate for repeat Guthrie cards was 0·27%, but with minor changes in the assay technique it fell to 0·12% in the second half-year.

Fifty babies had initial TSH concentrations over 80 mU/l, and in 23 (46%) the diagnosis of hypothyroidism was confirmed; the 27 high false-positive results were largely due to technical problems in the early phase of the project. Thus the cut-off at 80 mU/l resulted in 88% of the hypothyroidism cases being rapidly identified, but routine recall for serum sampling on the basis of a single spot TSH concentration over 80 mU/l would have resulted in an unacceptably high false-positive rate for serum sampling. Of the 34 babies recalled for serum sampling, 26 were confirmed as being hypothyroid while eight gave normal results. The normal results were obtained mainly in babies recalled because of the poor quality of repeat specimens. Table I gives details of the results of screening.

TABLE I—*Numbers of babies in whom repeat Guthrie tests carried out and serum sampled and numbers of cases of congenital hypothyroidism (CH) diagnosed according to initial TSH concentration (87 444 babies screened)*

TSH at initial screening (mU/l)	No in whom Guthrie test repeated	No of cases of CH
<25	0	0
25-80	182	3
>80	50	23
Total	232	26
No in whom serum sampled	34	

CONFIRMED CASES OF HYPOTHYROIDISM

We detected 26 cases of primary hypothyroidism, as judged by a persistently raised serum TSH concentration that was suppressed by treatment, giving an incidence of 1:3363. Seven of the babies were boys and 19 girls (M:F = 1:2·7). In none of these cases was there a history of prenatal exposure to excess iodine or goitrogens. Postmaturity was common, 13 of the babies being born after more than 41 weeks' gestation; in 19 cases labour was induced, and six of the babies were born by caesarean section. The mean birth weight was above average (3600 g; range 1530-5000 g).

Only two cases (7·7%) had been diagnosed by conventional methods by the time the results of screening became available, one because of functional intestinal obstruction and the other because of pronounced clinical signs of hypothyroidism. Nine babies (35%) had feeding problems (slow feeding, vomiting, poor weight gain), and these symptoms had delayed hospital discharge in two cases and led to readmission in another. Three babies were still jaundiced (serum bilirubin concentration above 170 μmol/l (9·9 mg/100 ml)) at 3 weeks and 10 babies (38%) were jaundiced after 10 days. Other symptoms reported included constipation (seven babies; 27%) and a hoarse cry (five; 19%). Six babies (23%) were considered to be asymptomatic by their mothers, although two had fairly pronounced signs of hypothyroidism.

Although the typical facial appearance of cretinism was present in only a few babies, subtle early signs of hypothyroidism could be detected by careful clinical examination in the majority. Small goitres were palpable in two babies (8%), and in several the trachea was easily palpable, suggesting the absence of a normally sited thyroid gland. An umbilical hernia was present in nine babies (35%); macroglossia in four (15%); large fontanelle in six (23%); and hypotonia in four (15%). No signs were observed in seven cases (27%). Two babies had other complications: one was extremely light for dates (1520 g at 38 weeks' gestation) and the other had microcephaly, brachydactyly, corneal opacities, and Hirschprung's disease.

The biochemical severity of hypothyroidism varied considerably (table II), and the thyroid function tests generally correlated well with the amount of thyroid tissue seen on the scan. Twenty-one babies

TABLE II—*Biochemical findings in 24 cases of congenital hypothyroidism grouped by bone age. Figures are mean concentrations (and ranges)*

Bone age* (weeks)	No of cases	TSH (mU/l)	T4 (nmol/l)	T3 (nmol/l)
<36	12	775 (155-1760)	27·8 (5-84)	1·25 (0·05-3·7)
36-40	4	495 (106-1230)	59·5 (35-86)	2·85 (1·23-4·70)
>40	8	219 (47·5-925)	65·8 (34-136)	4·02 (2·75-6·10)

*Bone age by comparison with standard plates (Pyle and Hoerr), using left knee.
Conversion: SI to traditional units—T4: 1 nmol/l ≈ 0·08 μg/100 ml. T3: 1 nmol/l ≈ 0·65 ng/ml.

(81%) underwent ^{123}I thyroid scanning. An ectopic thyroid was the most common finding (11 babies (42%); seven with large thyroids and four with only remnants of thyroid tissue). Three of the babies had "compensated" hypothyroidism, with serum T4 concentrations in the low-normal range 86-113 nmol/l (6·7-8·8 μg/100 ml). Two babies (8%) were athyrotic. Three babies (12%), two of whom were not scanned, had goitres. Two of these babies probably had enzyme defects of thyroxine synthesis; the parents of one were first cousins, and the other had a family history of congenital goitre. The cause of the goitre in the third baby is unknown, but the hypothyroidism was only mild (serum T4 concentration 136 nmol/l (10·6 μg/100 ml) and serum TSH 80 mU/l). In seven babies (27%) the thyroid was in the normal position. Of these seven, one had a hemithyroid, three had apparently hypoplastic glands and two may have been transient cases.

Delayed treatment—Treatment was delayed in two cases. In one the baby was born soon after screening started, and although a spot TSH of 319 mU/l was obtained on the initial assay, another child was recalled through confusion over the name. When the repeat result was normal the initial high value was wrongly ascribed to a technical error as a result of inexperience. We have now modified our procedure to try to eliminate this type of error. In the other case an inadequate Guthrie card was submitted with an incorrect home address, leading to considerable delay in our receiving the repeat specimen.

Treatment and follow-up—When the two cases in which treatment was delayed are excluded, the mean age at starting treatment was 32 days (range 21-57 days). The thyroid scanning delayed treatment by a maximum of four days because of the limited availability of ^{123}I. With experience the mean age at starting treatment is falling, but 21 days is the earliest possible time with our programme. Treatment was started with 25-50 μg of L-thyroxine/day. Serum T4 and TSH concentrations were rechecked after two to three weeks and the baby usually then referred to a local paediatrician for follow-up. We plan to reassess all the cases ourselves at the age of 1 year, temporarily withdrawing treatment and repeating the TSH, T4, and T3 estimations. This should identify any transient cases. Griffiths Developmental Assessment will be carried out at 1 year, and long-term evaluation of intelligence, behaviour, and neurological development is planned.

FALSE-POSITIVE CASES

Of the 182 babies in whom Guthrie tests were repeated because of initial TSH concentrations between 25 and 80 mU/l, only four yielded abnormal results. Three of these babies were mildly hypothyroid and were treated, while the fourth had a persistently slightly raised TSH concentration (16·5 mU/l), which returned to normal at 16 weeks without treatment. This group probably included several babies with abnormal activation of the thyroid-pituitary axis leading to prolongation of the TSH surge that occurs soon after birth.[8] Relatively low spot T4 concentrations were obtained in many of these babies, who could possibly be considered to have had "transient hypothyroidism."[9] The mean (±SEM) dried blood-spot T4 concentration (serum concentration is about twice blood-spot concentration) is 63·2 nmol/l (4·9 μg/100 ml) at the 20th percentile for a normal population (data from East Anglian Regional Screening Programme); and was 42·6±2·7 nmol/l (3·3±0·2 μg/100 ml) in 22 infants of normal gestation with transiently raised TSH; 37·4±3·7 nmol/l (2·9±0·3 μg/100 ml) in 18 preterm infants with transiently raised TSH; and 24·5±4·3 nmol/l (1·9±0·3 μg/100 ml) in eight cases of confirmed hypothyroidism.

Further evidence for transient hypothyroidism comes from the clinical data (tables III and IV) obtained by the health visitors when the repeat Guthrie tests were collected, showing that a high proportion of these false-positive results were from small, preterm infants. There was no particular association with the mode of delivery or feeding. More knowledge is required to judge whether treatment is indicated in these infants.

TABLE III—*Birth weights of infants with transiently raised TSH concentrations (false-positive cases)*

Birth weight (g):	<1000	<1500	<2000	<2500	<3000	<3500	<4000	≥4000
Cumulative % (n=71)	1·4	16·9	25·4	36·7	56·4	76·1	90·2	100
Expected cumulative %*	0·4	1·0	2·2	6·8	25·7	64·7	91·6	100

*From *British Births 1970*.[17]

TABLE IV—*Gestational ages of infants with transiently raised TSH concentrations (false-positive cases)*

Gestation (weeks):	<28	<30	<32	<34	<36	<38	<40	≥40
Cumulative % (n=61)	1·6	4·8	14·6	22·8	31·0	47·4	87·5	100
Expected cumulative %*	0·4	0·9	1·4	2·6	6·0	19·6	63·1	100

*From *British Births 1970*.[17]

Discussion

Although the first screening programme used a T4 assay alone,[1] it is now clear that this may miss some babies with ectopic glands in whom T4 concentration may be in the low-normal range.[10] Thus most screening programmes use a T4 assay followed by a TSH assay in patients with low-normal values, or TSH assay alone. We chose TSH assay as the primary screening method because of the economy of a one-step method and because we thought that the recall rate for false-positive results would be low. While the TSH method does not detect secondary (pituitary or hypothalamic) hypothyroidism, cases of this are uncommon (1:60 000 to 1:100 000)[3] and there is no convincing evidence that the patients are at risk for mental retardation. We saw no advantage in detecting deficiency of thyroid-binding globulin, a condition associated with normal thyroid function but low serum T4 concentrations. While the TSH assay takes longer than the T4 assay, it takes less time than the combined T4 and TSH method. The technical difficulties were not as great as is sometimes suggested; only three of the assays were unsatisfactory, with a higher incidence of false-positive results.

Either cord-blood specimens or dried blood spots on Guthrie cards have been used in most screening programmes. As the department already had a well-established screening programme for phenylketonuria, we chose to use the spare spots on the Guthrie cards, with the staff responsible for the Guthrie tests punching the blood discs and preparing the assay tubes. As the blood samples are taken about seven days after birth a diagnosis of congenital hypothyroidism will be made about one week later than is possible with cord-blood screening. We thought, however, that the advantage of using an established system for collecting specimens heavily outweighed the drawbacks of a week's delay in obtaining the screening results. A further short delay arose because we reassayed specimens that gave high results on the first assay to reduce the number of unnecessary recalls. This could only have been avoided by performing the assay in duplicate, as in the Swiss programme, but this would have added to the costs and the recall rate for inadequate specimens. We still do not know how important such delays are for mental development, but we now aim to start treatment by at least 1 month of age if possible.

We believe that the mass application of TSH radioimmunoassay is feasible in the United Kingdom but that it is vital that the method should be supervised and controlled by staff who have experience in radioimmunoassay techniques. In addition the assay should be closely linked to a separate assay for serum TSH, as the screening assay may be inaccurate if not continually cross-checked against a conventional serum assay. When screening becomes more widespread quality-control reference spots for use by different centres would be desirable. One of the major advantages of TSH screening is the substantial margin for error that the technique permits, high values being between 10 and 150 times the normal value. Treatment is apt to be delayed even with perfect assay techniques owing to administrative error, and for this reason the systems for handling specimens and recalling patients should be as simple and direct as possible. Automated data-processing methods reduce the risks still further. Despite many inquiries, we have not learned of any cases of delayed treatment other than the two described. Nevertheless, clinicians should continue to ask for thyroid function tests regardless of the screening result if they suspect that an infant has hypothyroidism.

Any screening programme allows for diagnostic tests and treatment to be centralised. We thought that there were several advantages in performing the confirmatory tests ourselves and initiating treatment before referring the patients to their local paediatricians for follow-up. In particular, this avoided delay in starting treatment and permitted full evaluation of the degree of hypothyroidism in each case. We shall also coordinate the reassessment of thyroid function at 1 year and arrange for long-term developmental follow-up.

The relatively high incidence of congenital hypothyroidism in this programme (1:3363) is similar to that found with other TSH screening programmes[10] and about double that found in retrospective studies in Holland[11] and Sweden.[12] This large difference is probably due not to geographical variation in the incidence of the condition but to the fairly high proportion of mild cases that are detected by TSH assay. Some of the babies with ectopic thyroid glands would probably have had compensated hypothyroidism for several months or years and would have been classified as cases of juvenile hypothyroidism. Thyroid function declines steadily, however, in patients with ectopic glands,[10 13] and we believe that such patients should be treated as soon as the diagnosis is established.

Can we make any estimate of the likely benefits of the first year of this screening programme? We have no doubt that it has led to early diagnosis and treatment in a considerable number of children with congenital hypothyroidism. In the area screened the diagnosis of this condition by clinical methods has often been delayed, only 40% of cases being recognised before 3 months of age (JAH, unpublished data). This is similar to the pattern in other European countries such as Sweden,[12] and, contrary to our earlier views,[14] we doubt whether this will be appreciably improved by educating health-care workers further. The prognosis for intellectual development has also been

poor, about one-third of children with congenital hypothyroidism in the area requiring special schooling and one-quarter having IQs of less than 70 (JAH, unpublished data). The prognosis for mental development is generally accepted to be better when treatment is started early,[15 16] and while it will be several years before we can fully assess the outcome in our cases, results from other screening programmes encourage us to believe that the prognosis has been improved in most of them.

Thus the first year of this pilot project confirms that TSH screening for congenital hypothyroidism linked to Guthrie screening for phenylketonuria is reliable and feasible, and we expect that introducing screening on a national basis would considerably improve the prognosis for many children with the condition.

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Addendum

Reassessment at 1 year has confirmed one transient and six permanent cases of hypothyroidism. Hence, we estimate that the incidence of transient hypothyroidism will not exceed 10%.

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ONE HUNDRED YEARS AGO The *Pall Mall Gazette* of the 24th February, "as an example of what may happen under the present lunacy laws, and of what does happen, it may be feared, oftener than is imagined," quotes an incident reported to it by an anonymous correspondent; and in doing so, affords a good example of what may happen, and does happen, it may be feared, oftener than is imagined in the present crusade against the lunacy laws. The incident, in the words of the narrator, is as follows.

"A friend of mine had been exposed to the rigour of a severe snowstorm, and when the subsequent depression passed off and reaction set in, the doctors mistook delirium for dementia, and hurried him off to a private asylum in a most indecent haste, to the dismay of some of his friends, who were at a distance, and who got him out after some trouble. Taking the responsibility on themselves, they took him to London, where they got the advice of the highest medical authorities in these cases, who certified that he not only was quite sane, but had not any symptoms of ever having been otherwise. I am glad to add that he is now as well as he ever was in his life."

This story is evidently too vague and deficient in detail to enable any judgment to be formed, whether the circumstances which it recounts do really cast discredit on the medical men engaged in the case or on the lunacy laws. Delirium, due to reaction following upon depression subsequent to exposure to the rigour of a severe snowstorm, is an exceedingly rare malady in this, and, indeed, in any country, and medical men might well be excused had they mistaken it for something else. But there is no evidence that they did so; for what is here called delirium is really acute mania of an intense type, due probably to paralysis of the vaso-motor nerves of the head and neck, and congestion of the brain, and requiring prompt and vigorous treatment. It is not to be supposed that the mental derangement produced by exposure to cold is a slight and transient delirium like vinous intoxication: on the contrary, it is characterised by violent excitement and restlessness, destructive propensities and objectionable habits, and is generally fatal, sometimes in as brief a period as forty-eight hours. The gentleman referred to in the *Pall Mall Gazette*, therefore, instead of grumbling at his doctors, ought, it seems, to feel thankful to them for conducting him safely and expeditiously through a very formidable illness. Most persons would think life cheaply purchased at the cost of a short detention in a lunatic asylum; and it is not at all unlikely that the sufferer from cold-stroke really owed his recovery to the care and appliances of the asylum and the treatment that he there received. On the other hand, he might have recovered quite as rapidly in the place where he was attacked; and this is obviously what he and his friends think would have occurred had he been left alone, but it is easy to be wise after the event. The doctors had probably a raving and dangerous lunatic before them; they saw no signs of any abatement of his malady, and in good faith (for no sinister motive is alleged against them) they did what they thought best for his safety and recovery, and perhaps for the safety of others also. Their patient is now "as well as he ever was in his life," and turns to rend them. It is said that the doctors acted with "indecent haste"; but that is a relative term, and what is indecent haste to one person may be unjustifiable delay to another. Of course, in cases of acute insanity, it is advisable, when practicable, to give home-treatment a fair trial; but everything depends on the nature of the insanity, the means of the patient, and the circumstances in which he is placed. A dozen sets of circumstances are conceivable, in which removal to an asylum ought to be as prompt as possible. Suppose that a gentlemen of small income who has not been drinking is suddenly seized in a hotel where he is living with violent mania, in which he smashes the furniture, attempts suicide, threatens murder, and disturbs and alarms the other inmates, will any one argue that there would be impropriety in putting him in an asylum as quickly as possible?

It is possible that the case referred to by the correspondent of the *Pall Mall Gazette* is a glaring instance of defects or "undue facilities" in the lunacy laws, which certainly require amendment in many directions, or of gross abuse of the existing provisions of these laws. But, on the other hand, it is possible that it is merely an instance of one of those personal grievances that will occur from time to time under the best of laws, and that no legislative foresight is equal to avoid. Only a meagre outline of it has been presented; but it seems to amount to this, that a gentleman when temporarily insane was placed for his good in a private lunatic asylum, and that, having recovered, he is much annoyed at the event. The grievance of which he has to complain, however, is surely not greater than that of an innocent person who has been imprisoned while awaiting trial because found in suspicious circumstances. (*British Medical Journal*, 1880.)