

Outcome for congenital hypothyroidism

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SUMMARY In a study designed to provide retrospective control data for a neonatal thyroid screening programme, the problems of 141 hypothyroid children were examined. The mean IQ (Wechsler intelligence scale) was 79.5 for children with congenital hypothyroidism but was normal in 6 children diagnosed before age 6 weeks. Diagnostic delay was associated with a steady decline in mean IQ but there was an improvement in some late diagnosed cases. A strong association was found between IQ and parental social class. Twenty five percent of the children were mentally retarded and 29% were at special schools; 54% of children at normal schools and 43% at special schools showed deviant behaviour. Other problems included clumsiness (26.2%) and squints (26.2%), and these were more common in children with a lower IQ. Congenital hypothyroidism is associated with persistent morbidity in many aspects of cerebral function. The adverse effects of prenatal hypothyroidism are largely reversible if treated before age 6 weeks.

Neonatal screening for congenital hypothyroidism (CH) has been progressively introduced throughout North America, Japan, and Europe over the past five years and is now also universal in the United Kingdom. In none of these screening programmes has it been considered ethical to conduct any controlled trial of the value of screening itself. Thus the assessment of the results depends in part on comparison with retrospective studies of children with clinically diagnosed CH. Because previous retrospective studies had shown an improvement in mean IQ with earlier diagnosis,^{1 2} screening was expected to be effective in preventing mental retardation and reversing the effects of intrauterine hypothyroidism. Some doubts were, however, expressed by McFaul *et al.*³ as to whether screening would be fully effective in preventing all the long term complications of CH. In particular they found that some children diagnosed between 4 and 10 weeks of age had evidence of clumsiness, visual disorders, learning difficulties, and behaviour problems. The present study was undertaken to see if these findings were representative of an unselected group of children with CH and also to provide up to date retrospective data for comparison with children diagnosed by screening.

Patients and methods

Altogether 141 hypothyroid children were included in the study. The names of 98 children were

obtained by writing to all the paediatricians in the four Thames health regions. To ensure that other handicapped hypothyroid children were not missed, the 21 area health authorities in these regions were asked to supply the names of children with CH from the handicap registers, and this produced 41 more children. Two children were found who were in long stay mental hospitals. While the handicap registers gave the names of only 4 children who were not seeing a paediatrician regularly, they helped considerably in tracing children who were attending hospital clinics.

Data on the mode of presentation and confirmatory tests were obtained from the case notes. The age of diagnosis was taken as the date on which treatment was actually begun. For bone age estimations, the original radiographs were compared with standard plates.^{4 5}

Examination of the children. The 141 children were seen once with their parents either at home or at the hospital they usually attended. Testing took up to two hours and was performed in a standard order.

Intellectual assessment. For children aged over 6 years the Wechsler intelligence scale (WISC-R) was used with the British amendments; children aged between 4 and 6 years were tested with the McCarthy scale of children's abilities and younger children were tested with the Griffiths scale.

Assessment of attainment. Reading ability was tested

with the Neale analysis of reading ability (Form A), writing was assessed by asking the child to write his name and address and by seeking parents' and teachers' opinions, and mathematics by the appropriate sub scale of the intelligence test.

Behaviour. Parents and teachers were asked to complete the Rutter A⁶ and Rutter B⁷ scales respectively. In addition, for those children attending normal school, class teachers completed the Rutter B form for two control children of the same sex and nearest in age to the named child.

Physical and neurological examination. The neurological examination was based on the methods of Touwen and Prechtl.⁸ Visual acuity was determined and the eyes examined for squint, nystagmus, and quality of visual pursuit. Three tests were used for examining eye-hand coordination and fine motor control: bead threading—the time taken and ability to thread four coloured beads on to a wooden stick with each hand after a demonstration and practice; finger successive movements—the time taken to complete 20 successive finger movements, touching the tip of each finger with the tip of the thumb; and the posting box—the time taken to insert 6 plastic shapes into a simple posting box (Kiddicraft Ltd). Age related normal values were available for these tests^{3 9 10} and their validity was confirmed with some normal and sibling controls. The results were used to establish a motor score for each child. Any test which the child took longer than +2SD from the normal mean to complete, received a score of +1. Thus a motor score of 0 to +3 was obtained and children scoring +2 or +3 were considered to be 'clumsy' (Table 1).

The children were also examined for cerebellar dysfunction with the finger-nose test; for problems of balance by one leg standing, straight line walking, walking on tiptoe, and hopping. The physical examination included palpation of the thyroid, and an assessment of muscle tone and limb reflexes.

Table 1 *Relation between motor score, age, and IQ in 103 children with hypothyroidism*

Motor score	0	1	2	3	2+3
No	46	30	18	9	27
%	44.7	29.1	17.5	8.9	26.2
Age at test (yrs)					
Mean	11.3	10.9	9.5	7.8	9
SD	2.94	2.94	2.86	2.01	2.58
IQ (WISC-R)					
Mean	93.4	84.8	66.4	65	65.9
SD	18.0	12.4	18.7	11.3	16.2

Motor score is the number of tests of dexterity for which the children took longer than +2 SD to complete, using age adjusted norms.

Diagnostic classification. As very few children had had investigations performed to establish aetiology, arbitrary definitions of CH were necessary. Altogether 111 (79%) were treated before 2 years of age and were thus considered to have CH. Of these, 10 children came from families with more than one affected child and were called 'familial'. Of the 30 late onset cases, 15 had clear evidence of onset from symptoms or bone age well before age 2 years and were therefore also thought to be cases of CH, six were familial, five probably had acquired hypothyroidism, and in four the aetiology was not clear. Thus, including the familial cases with probable dysmorphogenesis, 132 children were thought to have CH.

Results

Age and sex of the children. The children's ages ranged from 1 to 16 years at the time of examination, but 101 (72%) were over 6 years, at which point IQ testing becomes more accurate. There were more girls than boys in the CH group (33 boys, 83 girls; ratio 1:2.5) but more boys than girls in the familial group (9 boys, 3 girls; ratio 3:1).

Social class and ethnic origin. The children came from a wide variety of backgrounds—inner and outer London, small and large town, and rural. This variety was also reflected in the social class distribution, classified by paternal occupation: 9.3% were social class I, 23.6% class II, 9.3% class IIIN, 35% class IIIM, 10.7% class IV, 9.3% class V, and 2.9% were unclassified. In comparison with figures from the 1961 Census and 1976 Register of births, this represents a 7 to 14% excess in classes I and II and slightly fewer in the other groups. This may be caused by a genuine difference in the social class structure of London and the surrounding areas, or a demographic change in the population. Altogether 128 (90.8%) were of white British ethnic origin, 6 (4.8%) Irish, 4 (2.8%) Asian, and 4 (2.8%) from other countries.

Family structure. There was a slight excess of mothers aged between 30 and 39 years at the time of the child's birth compared with the Registrar General's returns for 1967, 1972, and 1977, but no associations were observed with paternal age and neither did the family position of the children deviate from that seen in the Registrar General's returns. There were three sets of twins (one was stillborn, anencephalic) but in no cases were both twins affected.

Gestation, labour, and delivery. As judged by

maternal dates only 6 (4.8%) of births were preterm but 37 (29.4%) births were after term. Fifty one percent of labours were induced, but despite this most deliveries were otherwise normal; the percentage delivered by caesarean section was 13.2%. Birthweight was mean (SD), 3.339 (0.648) kg ($n=137$); in only 8 (5.8%) was the birthweight below 2.5 kg and 19 (13.9%) weighed over 4.0 kg.

Presentation. A total of 102 (72.2%) had symptoms in the neonatal period that were possibly related to CH. These included feeding difficulties (48%), constipation (23%), prolonged jaundice (23%), and lethargy (18%). The neonatal symptoms lead to the diagnosis in only 52 (36.9%) children. The later diagnostic features included developmental delay (26%), hypothyroid facies (15%), short stature (14%), and failure to thrive (9%). Diagnostic delay was very common: only 32% were diagnosed by age 3 months and 66% diagnosed by 1 year. The cause of late diagnosis was delayed referral—only two children had substantial delay after being seen by a paediatrician. There was no appreciable improvement in the mean age of diagnosis over the years 1963–76, and considerable delays were still occurring for children diagnosed within the period 1973–8.

Confirmatory investigations. Confirmatory thyroid function tests were available in 117 (83%) children only, but the others were not excluded provided the presentation was classic and there was supporting evidence of CH. The protein bound iodine value was mean (SD), 1.7 (1.36) $\mu\text{g}/\text{dl}$ ($n=65$), serum thyroxine concentration was mean (SD), 26.4 (25) nmol/l ($n=53$) and a raised thyroid stimulating hormone value was recorded in 42 children. A retarded bone age (Greulich and Pyle) was recorded in 99 children but often only a wrist radiograph had been taken which is of limited value in young children. Of those in whom bone age estimations were done the results were prenatal in 29% and less than 3 months in 60%.

Aetiology of the hypothyroidism. Neither social class nor parental age seemed to be important factors in the aetiology of sporadic hypothyroidism. Very few mothers reported taking drugs during pregnancy, only two reported early bleeding, and two had proved rubella infection (aetiologically linked in one case). Of the 16 familial cases, at least 8 had definite biosynthetic defects, three had easily palpable goitres, and five had had confirmatory uptake studies. No children had had thyroid scans.

Prevalence of CH. Retrospective figures were calcu-

lated for three geographic areas for the period 1965–78. These were: Kent Area Health Authority (AHA), 48 cases in a childhood population of 319 900 (1/6700); East Sussex AHA, 17 in 11 400 (1/6700); Essex AHA, 35 in 243 600 (1/9400). The figures for Kent AHA were probably the most complete since all children with hypothyroidism in Kent are thought to have been included in the study. Thus the minimal retrospective prevalence is about 1/7600.

Developmental progress. The timing of four major developmental milestones was recorded from contemporaneous notes rather than the mothers' subsequent report. The age of sitting alone was recorded for 95 children. Of the children who were sitting by age 10 months, 50% had WISC IQs over 90 and only two were mentally retarded. On the other hand, 7 of the 8 children who did not sit till after 18 months were mentally retarded. Delay in walking became a poor prognostic indicator only after 18 months and walking after the age of two years was associated with mental retardation in 55.6% of subjects. The age at which three clear words with meaning were said was recorded in 97 children. Mental retardation became strongly associated with speech delay only beyond 30 months (80% with IQs below 70) and less severe degrees of speech delay were not associated with poor intellectual prognosis. The age of speaking in sentences was, however, the best developmental discriminator for final IQ—all those speaking in sentences before age 2 years had IQs over 90 and none who did not use sentences till after 4 years had IQs above 70. Altogether 42 children (34.7%) had been referred for speech therapy.

Intellectual assessment. Ten young children were assessed with Griffith's scale and had a General intelligence quotient of mean (SD), 83.9 (11.2) (range 71 to 106). They showed patterns of general motor and speech delay but no specific deficits were apparent.

The McCarthy scale was completed by 21 hypothyroid children with ages ranging from 3 years 3 months to 8 years 3 months. The General cognitive index was mean (SD), 81.7 (22.8) (range <50 to 120). There was no statistical significance at the 5% level between the results of sub-test scores.

The WISC-R test was completed by 99 children. The mean IQ for the CH group (79.5) was significantly lower than that for the 14 familial cases (95.4) or the 5 acquired cases (92). The distribution of WISC IQs is shown in Fig. 1: 25.3% had IQs below 70, and 30.3% were above 90. When the WISC-R IQ was related to the age at the time of diagnosis (Fig. 2), there was a steady decline in mean IQ with

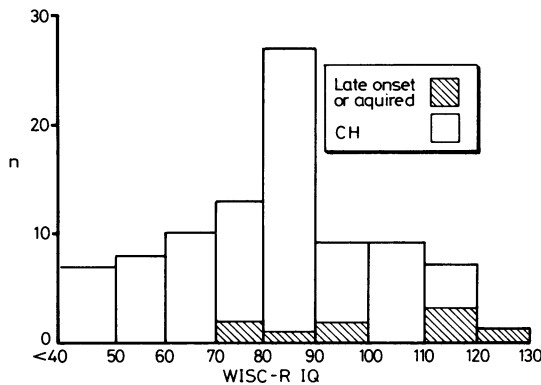


Fig. 1 Distribution of WISC-R IQs.

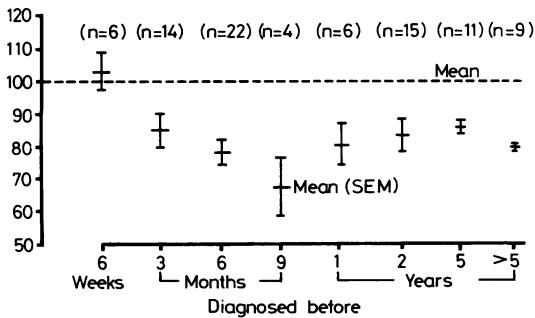


Fig. 2 Relation between age of diagnosis and WISC-R IQ.

diagnostic delay over the first 9 months, followed by a slight improvement. At all ages the familial group had a better outcome than the CH group. The best intellectual prognosis was for those children diagnosed before 6 weeks. The distribution of IQs at different diagnostic ages showed similar trends; none diagnosed before age 6 weeks were mentally retarded compared with 75% of those diagnosed between 6 and 9 months. Five of the children diagnosed before 3 months of age were known to have a prenatal bone age and their IQ was mean (SD), 94.4 (19.5) showing that a good intellectual outcome is possible even with intrauterine hypothyroidism.

A difference of more than 15 points between the Verbal and Performance scales was present in 28 (29.5%) of the children. In 20 the verbal IQ was greater and these children tended to have higher Full scale IQs (mean (SD) 91.3 (18.4)). For the sub-scales the highest mean scores were obtained on Block design and the lowest on Coding.

Mean IQ was strongly related to parental social class. The mean IQ for social classes I and II was 90.5 (n=21); for social class III it was 79.8 (n=38), and for social classes IV and V was 64.2 (n=13). There was an increasing fall in the mean IQ from the normal population from social classes I and II (18.5%) to IV and V (34.8%). The distribution of IQs related to social class is shown in Fig. 3.

Schools. Of the 112 school age children in the study, 32 (28.6) were attending special schools. Twenty three of these children were at educationally subnormal (ESN) (M) schools, two were at ESN (S) schools and three in residential schools. Of the 80 children attending normal schools, 33 (28.8%) were in remedial classes for at least one subject so that only 57 children (50.9%) were receiving normal education.

Attainments. Ninety seven children were of a suitable age for testing reading ability on the Neale scale. Fourteen (14.4%) were unable to read and a further 15 (15.5%) had more than two years delay in reading age for both accuracy and comprehension. Thus 30% of these children had a reading problem. Their IQ was mean (SD), 72 (17.8). These results agreed well with those of the teachers' questionnaires, which scored 26% as having a reading problem compared with 3.8% of 72 matched controls. The parents, however, underestimated the extent of the reading difficulties. Many children also had problems with spelling and writing. The teachers considered that 47.9% had special writing difficulties (controls 17%) and 49.3% had special spelling difficulties (controls 22%). Only one child, however, seemed to have a specific learning disability: usually these problems were associated with



Fig. 3 Distribution of WISC-R IQs related to parental social class.

a more general cognitive deficit. Similarly the WISC-R Arithmetic scores did not suggest specific problems with this skill. Drawing skills also varied considerably, but many children had poor pencil control and immature styles.

Behaviour. Seventy three Rutter B behaviour questionnaires were completed by teachers for the CH children and 99 questionnaires for matched controls. Of the CH children, 28 (55%) of those at normal schools were rated as exhibiting deviant behaviour compared with 15.2% of controls. Of the children at special schools, 9 (41%) were rated as exhibiting deviant behaviour. For the CH children the sex differences were not significant, but more of the boy controls were rated as deviant. The relation between behaviour deviance and IQ is shown in Fig. 4. Behaviour deviance was two and a half times more common in children with IQs below 90 than in those with IQs above 90. The behaviour problems were more neurotic than antisocial in kind and included poor attention span, fearfulness, speech difficulties, and wetting or soiling at school. Parents also identified speech problems as being major areas of concern.

Neurological problems and clumsiness. Five children (3.5%) had cerebral palsy—in one this was probably the result of kernicterus. In four of these children there was also mental retardation and there was no clear relation with age at diagnosis. Two further children had severe retardation with notable autism. Nineteen (13.5%) had had convulsions, associated with fever in 12 (8.5%). On the parental questionnaires, 25.7% were thought to be 'very clumsy' and 48.3% to be 'of below average sporting ability'. Similar results were obtained from the teachers' questionnaires (controls 8%). A measure of clumsiness was obtained from the Motor score (Table 1).

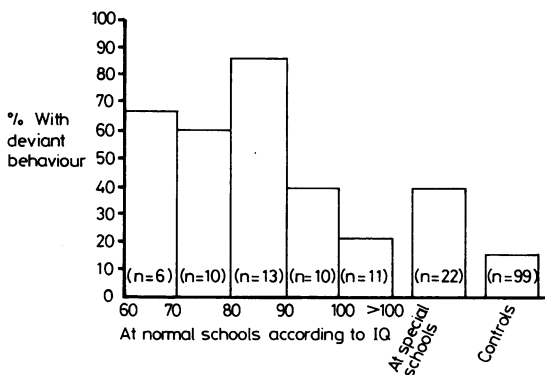


Fig. 4 Percentages of children with behaviour deviance.

The clumsiness was a feature of 26.2% of the children, was related to IQ, and tended to lessen with increasing maturity. None of the children diagnosed before 6 weeks were clumsy but 50% of those diagnosed between 6 weeks and 3 months were. Other motor problems included poor balance (8.5%), tremor (6%), and jerky hand movements (7%) None had classic cerebellar signs.

Visual problems. Two children had severe visual impairment that was unrelated to the hypothyroidism. A squint had been or was still present in 34 (26.2%), and 14 (10%) had had squint surgery. The squint was convergent in 15 children, divergent in 6, and alternating or complex in 7. Two children had severe amblyopia and three had nystagmus.

Other problems. Enuresis was a continuing problem for 21.3% of the children and persistent constipation a problem for 5.7%. Seven children had a hearing loss which was conductive in three and sensorineural in four, two of whom wore aids.

Growth and treatment. The height centile at the time of examination is shown in Table 2a. There was a shift to lower centiles that was more notable for the boys and at the time of puberty. This may reflect delayed pubertal growth. In contrast the head circumferences showed a consistent shift to higher centiles in both sexes at all ages (Table 2b).

The dosage of levothyroxine that the children were receiving was related to body weight and surface area. The mean dosage being given was 137 $\mu\text{g}/\text{m}^2$ which is higher than the usual recommended dose of 100 $\mu\text{g}/\text{m}^2$.¹¹ Ten percent were, however, having dosages which were more than twice or less than half this amount.

Table 2a Height centiles of children with congenital hypothyroidism at the time of examination

	<10th No %	10-50th No %	50-90th No %	>90th No %
Boys (n=43)	16 (37.2)	13 (30.2)	13 (30.2)	1 (2.3)
Girls (n=79)	22 (27.8)	30 (38.0)	19 (24.0)	8 (10.1)
Total (n=122)	38 (31.1)	43 (35.2)	32 (26.2)	9 (7.4)

Table 2b Head circumference centiles of children with congenital hypothyroidism at the time of examination

	<2nd No %	2-50th No %	50-80th No %	>98th No %
Boys (n=43)	1 (2.3)	12 (27.9)	23 (53.3)	7 (16.3)
Girls (n=77)	2 (2.6)	19 (24.7)	46 (59.7)	11 (14.3)
Total (n=120)	3 (2.5)	31 (25.8)	69 (57.5)	18 (15.0)

Discussion

Patient selection may have been an important factor in explaining some of the differences between previous studies of CH. For example, the mean IQ of 93.4 in a recent study,³ which is considerably higher than that found in the present study (79.5), may be explained by social class bias in hospital based series. For this reason one of the aims of this study was to find a group as representative as possible of the broad picture of clinical hypothyroidism in childhood. Thus 24 children for whom direct biochemical evidence of hypothyroidism at presentation was unavailable were not excluded. In all these children, however, other confirmative information included contemporary photographs, the presence of epiphyseal dysgenesis, and a raised serum cholesterol value. In view of the large social class effect found, distribution is very important and this was close to that of the general population. Also the home environments of the children were very variable; about one third came from London, one third from towns out of London, and one third from village or rural areas. The retrospective prevalence was similar to that of countries where comprehensive surveys have been undertaken (Sweden 1/6900,¹² Denmark 1/6064,¹³ and Netherlands 1/6000,¹⁴) suggesting that in the areas where a complete study was attempted, such as Kent, most clinical cases were detected.

It was not easy to assess the adequacy of treatment of these children. Many had not had thyroid function tests performed for some time but examination of the doses of levothyroxine being given suggested that about 10% were being significantly under or over-treated. How important this is for intellectual function is not known, but better treatment must be a factor in the steady improvement in mean IQ seen over recent years. For example, in Gesell's series of 1936¹⁵ the mean IQ was 61, and 25% had IQs below 45. The spread of IQs is still, however, very wide and biased towards the lower end. Two major influences on IQ have been identified—the age at which the diagnosis was first made and the social class of the parents. This kind of interaction is similar to that observed in light for dates infants in the National child development study.¹⁶ The reason for the strong social class effect is not completely clear but it was not just related to later presentation. Other possible factors include poorer compliance with treatment, poorer home environment, and less educational opportunity.

A clear difference was seen in outcome between children diagnosed by 6 weeks of age and 3 months of age, confirming recent reports.¹⁷ Data are similar to those summarised by McFaul and Grant from the

Table 3 Intelligence of children with congenital hypothyroidism treated before age 3 months (Data in brackets from MacFaul and Grant²²)

Age treated	No	IQs > 90 %	IQs < 75 %
Before 6 weeks	6 (18)	67 (55)	0 (11)
7–12 weeks	14 (47)	36 (36)	28 (38)

published reports (Table 3). It seems likely that there is a critical period in the first few weeks of human postnatal life for the effects of hypothyroidism on brain development. This is in keeping with the experimental evidence in rats showing a return to normal of brain configuration in young rats made hypothyroid at birth and treated at age 10 to 14 days.¹⁸

Behaviour deviance was rated by teachers to be three times more common in CH children than in controls, and the prevalence was higher than that for any other condition studied using the same technique.¹⁹ Attendance at a special school and an IQ over 90 were both factors which reduced behaviour deviance. The placement of a child of below average ability in a normal school seemed to be a major factor in behaviour problems.

Definite cerebellar ataxia was not observed in any children. Previous studies have shown a widely varying prevalence of cerebellar symptoms from 6%³ to 50%²⁰ but this probably results from problems of defining cerebellar ataxia. Many children had problems of motor coordination and a close relation was observed between clumsiness and both age and IQ, even with the use of age related norms. Thus the motor problems may be ones of maturational delay of the nervous system similar to the prolonged intellectual delay reported by Money.²¹

There are two important implications of this study for follow up programmes of neonatal thyroid screening. Firstly the problem of 'clumsiness' is bedeviled by subjectivity, poor definition of terms, lack of appropriate and agreed tests, and needs further research. Secondly, as it seems that most early diagnosed children are likely to have relatively subtle abnormalities, the selection of a large, well matched control group is of crucial importance.

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