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Congenital hypothyroidism:increased incidence in Asian families

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SUMMARY Screening in the North West health region of England showed a significantly higher incidence of congenital hypothyroidism in Asian families—1/918 compared with 1/3391 in non-Asians. This could only in part be explained by consanguinity. No differences were found in birth order, season of birth, gestational age, or birth weight between normal infants and those with congenital hypothyroidism. There was a significantly higher incidence of additional congenital abnormalities (9%) and a significantly increased mortality (5%) in infants with congenital hypothyroidism compared with unaffected infants.

Since the introduction of routine screening of the newborn for congenital hypothyroidism over the past 10 years, the incidence has proved to be considerably higher than previously realised at about 1/3500 to 1/3800.[1 2] It is even more common in preterm infants.[3] In addition, there has been speculation about ethnic differences in incidence,[4] season of birth,[5] increased morbidity and mortality,[6] an increase in associated congenital abnormalities including chromosomal abnormalities[7 8] (which is disputed[9]) that may delay the start of treatment,[6] and the presence of a thyroid growth limiting antibody in the mothers of infants with congenital hypothyroidism.[10]

In the North West health region of England 100 cases of congenital hypothyroidism have now been detected and they have been reviewed to see if the features listed were present.

Patients and methods

The North West health region had a population of 3 963 000 in 1985, which included a sizeable, mainly Moslem, Asian community. Screening for hypothyroidism by radioimmunoassay of thyroid stimulating hormone (TSH) was introduced in five health districts in November 1981, and the entire region was being screened by December 1982. One hundred cases of congenital hypothyroidism had been diagnosed in February 1987.

A blood spot from a heel prick is collected on to filter paper at the same time that the screening for phenylketonuria is done on the tenth postnatal day. A concentration of TSH of <20 mU/l is regarded as normal. If the concentration is between 20 and 40 mU/l a repeat sample is requested after checking. A concentration of >40 mU/l or a repeat value between 20 and 40 mU/l warrants formal investigation.

After a full history has been taken and examination carried out, the following investigations are done: measurement of serum concentrations of thyroxine, tri-iodothyronine, TSH, and thyroid autoantibodies in venous blood from the mother and the infant, an *x* ray to assess bone age, and a ^{99m}Tc radionuclide scan of the thyroid. If the diagnosis is confirmed treatment with thyroxine is started the same day. The local consultant paediatrician is contacted and asked to ensure follow up. The diagnosis is reviewed once at the age of 1 year when the child has not received treatment for one week after three weeks taking tri-iodothyronine. Thyroid function tests are then done to confirm permanent congenital hypothyroidism.

A few patients are not seen centrally when there are coexisting problems such as prematurity or other congenital abnormalities that require treatment elsewhere. Instead a full history is obtained by telephone where possible.

Population data were derived from three sources—firstly, the district birth returns that are collated at regional headquarters to allow for the differing periods each district has had screening for congenital hypothyroidism were studied. This permitted analysis by district, year of birth, sex, birth weight, gestation, and pregnancy number of all infants born in the region who survived the first 7 days of life and were thus eligible for screening. In addition, over

the same time period deaths from the age of 1 week to 1 year were also obtained.

Secondly, the number of Asian births was calculated from the birth registration returns for the region sent to the Office of Population Censuses and Surveys (OPCS) based on the mother's country of birth. This excluded mothers of Asian extraction born in the United Kingdom. There was little reliable official information relating to the racial origins of the United Kingdom population or whether a marriage was consanguineous.

Thirdly, the season of birth for the normal population was based on the 2 526 000 births in England and Wales during 1980 to 1984.[11]

Statistical analysis was by the Kolmogorov-Smirnov test for goodness of fit[12] and the χ^2 test, Fisher's exact test, and Poisson distribution as appropriate.

Results

From November 1981 to February 1987, 289 697 infants (51·6% of whom were boys) survived the first 7 days of life; 18 366 (6·3%) had mothers born in India, Pakistan, or Bangladesh (henceforward referred to as Asian). Congenital hypothyroidism was diagnosed in 100 patients of whom 77 were white, 20 were Asian, one was Arab, one was Jewish, and one was Chinese, but none was black. There was consanguinity in 11 Asian families, one Arab family, and one white family. The characteristics of the 100 infants with congenital hypothyroidism are shown in table 1. The incidence of congenital hypothyroidism in the region is shown in table 2. The difference in incidence between Asians and non-Asians is highly significant ($p<0·001$). The overall incidence (1/2897) is 1·3 times greater than the average in Europe (1/3800, $p<0·01$).[2] This excess is accounted for by the high incidence among Asians. The difference in the sex ratio between Asian and non-Asian (almost exclusively white) is not significant. One child with congenital hypothyroidism and multiple other congenital abnormalities was not screened (by oversight) and was diagnosed at the age of 3 months in another region.

Table 1 *Characteristics of 100 infants with congenital hypothyroidism*

Sex ratio (Male:Female)	1:2·7
Median (range) birth weight (g)	3365 (910–4760)
Gestational age (weeks):	
<37	9
37–40	44
>40	44
unknown	3
Median (range) time interval from birth to screen result (days)	16 (12–68)*
Median (range) time interval from birth to treatment (days)	19 (4–63)*

*One died before treatment started and three were treated before confirmation by screening.

Table 2 *Incidence of hypothyroidism in the North West region*

Race	*Incidence*	*95% Confidence intervals*	*Male: female ratio*
Asian	1/198	1/612 to 1/1670	1:5·7
Non-Asian	1/3391	1/2740 to 1/4396	1:2·3
Total	1/2897	1/2394 to 1/3621	1:2·7

There was no evidence of an abnormal seasonal variation in births of infants with congenital hypothyroidism. In the four quarters of the year, 25·6%, 19·5%, 28·0%, and 26·8% of infants with congenital hypothyroidism were born compared with 24·4%, 25·2%, 26·0%, and 24·4% for the normal population.

There was no difference in gestational age or birth weight of infants with congenital hypothyroidism and other infants in the region: 9·2% of infants with congenital hypothyroidism and 6·4% of other infants were born before 37 weeks' gestation, and 12·7% of infants with congenital hypothyroidism and 7·1% of other infants had median birth weights of under 2500 g.

There was no difference in the order of birth of infants with congenital hypothyroidism compared with others in the region.

Thirteen couples were identified as definitely consanguineous. The infants of consanguineous couples were 4·3 times more likely to have an anatomically normal or enlarged but normally placed thyroid gland on scan than the rest of the group ($p<0·03$), but the overall incidence of findings on radionuclide scans of the thyroid was similar to that found in Europe (tables 3 and 4).[12]

Nine infants had the following congenital abnormalities: trisomy 21 (n=2), multicystic kidneys, bilateral hydronephrosis, pelviureteric obstruction, ventricular septal defect, patent ductus arteriosus, pulmonary stenosis, pneumothorax, cleft palate, talipes equinovarus, and spastic diplegia. Two others had hyaline membrane disease. There was a high incidence of infants with trisomy 21—1/50—compared with the national incidence of 1/600 ($p<0·01$).[13]

These 11 infants were screened later than infants without additional problems. Five (45%) were screened by 20 days or older, compared with 19% of

Table 3 *Appearance of radionuclide scan*

	All families	*Asian families*	*Consanguineous families*
Aplastic	36	6	3
Hypoplastic	3	1	0
Ectopic	39	6	5
Normal	6	2	2
Enlarged, normal position	6	2	2
Unknown	10	3	0
Total	100	20	13

Table 4 *Association between scan type and consanguinity*

Consanguinity	*Appearance of scan*	
	Enlarged or normal	*Aplastic, hypoplastic, or ectopic*
Present	5	8
Absent	5	52
Total*	10	60

*All infants whose parents' marital state was known and who had a scan.

Table 5 *Causes of death in infants with congenital hypothyroidism*

Cause	*Sex*	*Age at death*
Fibrosing alveolitis	Female	3 years
Possible acute adrenal insufficiency	Female	6 weeks
Extreme prematurity	Female	4 weeks
Cytomegalovirus pneumonia	Female	5 weeks
Sudden unexpected death	Male	9 weeks
Down's syndrome and prematurity	Male	13 weeks

the uncomplicated group ($p=0{\cdot}07$), but they did not start treatment later than the group without complications, as all those with additional problems who were still alive were treated by 29 days of age compared with 90% of the group without complications. This compares favourably with a mean time to start of treatment of 32·4 days (range 8–108) for the group with complications described by Fernhoff *et al.*[6]

During the period November 1981 to February 1987, 1294 infants (0·46%) died aged 1 week to 1 year in the North West region (allowing for the differing screening periods for each district). Five (5%) of infants with congenital hypothyroidism died before the age of 1 year and one died at the age of 3 (table 5). This excess in mortality is significant ($p<0{\cdot}001$).

Discussion

Screening for congenital hypothyroidism in the North West health region is done comparatively late compared with other areas of the world[6] in order to coincide with the phenylketonuria screening,[10] which was established with a single community agency (health visitors) collecting the specimens on the tenth day of life. Less than 2% of infants are screened while still in hospital. The late timing of the screen may partly account for the lower detected incidence of transient hypothyroidism, which is 1/289 697 in this region compared with a reported incidence as high as 1/8000 in Europe.[1] The potential disadvantage of late screening is that infants with congenital hypothyroidism may then start their treatment late. Fernhoff[6] in Georgia, United States, screened infants between 2 and 7 days old and the mean date of starting treatment was 19 days (range 2–55) in a group without complications, compared with the median in the present study of 19 days (range 2–63, including the group with complications), suggesting little effective delay.

The results suggest that the children of Asian families are at greater risk of congenital hypothyroidism than the rest of the population. The total number of Asian births, however, does not include those mothers of Asian origin born in the United Kingdom as this information is not available. Nevertheless, the total number of identified Asian births would need to be doubled for the difference to lose its significance, and such under-reporting is most unlikely. It is not clear from the results why the Asian population has a high incidence of congenital hypothyroidism. An enlarged or normally placed thyroid on scanning was more common in families with consanguinity, but although 55% of Asian infants with congenital hypothyroidism were of consanguineous origin, less than half of the infants of consanguineous marriages had normally situated thyroids.

This suggests that currently recognised recessively inherited enzyne abnormalities do not account for the entire incidence in Asian families. If all consanguineous families are removed from the calculations the incidence in Asian families becomes similar to that in the white population. It would be interesting to know the incidence of congenital hypothyroidism in the Hindu or Sikh populations where consanguineous marriages are less common.

The suggestion that there is a maternal antibody blocking fetal thyroid genesis induced by TSH[10] in mothers of infants with congenital hypothyroidism with or without aplastic thyroids[14] prompted us to review the birth order. Van der Gaag *et al*[10] suggested that thyroid growth blockers may arise

not due to autoimmunisation but because of the presence of the fetoplacental unit. If (in the manner of Rh haemolytic disease) increasing numbers of pregnancies increase the potential for appreciable sensitisation, then infants with congenital hypothyroidism ought to have a higher birth order number than the rest of the population. The close similarity in the birth order of infants with congenital hypothyroidism and the general population, however, does not support this hypothesis.

Miyai *et al*[5] found an increased incidence of congenital hypothyroidism in babies born during the summer months; we did not confirm this, the summer incidence being similar to that in autumn and winter.

These results confirm the higher mortality and morbidity noted previously,[6–8] especially the high incidence among infants with Down's syndrome.[15] It is essential that screening of these infants for hypothyroidism (when they are often still in hospital and not being fed on the tenth day, and thus perhaps not being screened for phenylketonuria either) is not overlooked, as a delay in treatment in this group may be even more crucial.[2]

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