

Feasibility Study of Congenital Hypothyroidism Screening Programme at Maternity Hospital Kuala Lumpur

S O Sakinah, FRCP*, B A K Khalid, FRCP*, A Roslan*, A G Zainal*, M L Ng, PhD**, N Adeeb, FRCOG***, *Departments of Medicine, **Biochemistry and Obstetrics and ***Gynaecology, Universiti Kebangsaan Malaysia, 50300 Kuala Lumpur

Summary

Congenital hypothyroidism (CH) occurs with a prevalence of 1 in 2,000-4,000 live births. It is the main cause of mental retardation where early treatment results in normal IQ. Newborn screening for CH is now routine in developed and some developing countries.

We conducted a CH screening programme at Maternity Hospital Kuala Lumpur from June 1992 to May 1993 using cord blood thyrotropin (TSH) and thyroxine (T₄). 9,402 cord samples were examined, representing 39% of the total deliveries. Serum (T₄) was low (below mean -2SD) in 0.96% where in the majority of cases (94%) the TSH were normal. There was poor correlation between T₄ and TSH. TSH was high in 1.2% where in the majority of cases T₄ was normal. High TSH and low T₄ were detected in 0.04%. In the sample with high TSH, there was significant inverse correlation with T₄. This suggests that TSH is more appropriate as a primary screening test compared to T₄. The response rate for reexamination was only 52.1%. A high percentage of missing samples and low attendance rate for reexamination contributed to the failure of this study to determine the incidence of CH.

Our study has identified problems for CH screening. It suggests that before we introduce the screening programme in Malaysia, practical problems relating to cost-benefit analysis in planning, starting, funding and maintaining a mass screening programme should be seriously considered.

Key Words: Screening, Congenital hypothyroidism

Introduction

The prevalence of congenital hypothyroidism is about 1 in 2,000-4,000 births. It is one of the main causes of reversible mental retardation. The clinical diagnosis during the early neonatal period is difficult and often missed. The diagnosis is confirmed by low serum thyroxine and high serum thyrotropin (TSH) levels. The fact that CH is easily curable if diagnosed early during the neonatal period justifies the need for early detection. Treatment initiated within 45 days of birth usually

results in normal intelligence^{1,2}. Newborn screening for CH is now routine in the United States, Canada, Western Europe, Japan, Australia and New Zealand^{1,3}. CH screening has also been developed in several countries in South America, Asia and Africa, but most countries in these regions do not have screening programme for CH due to economic constraint and other factors. The WHO has called for worldwide screening for CH especially in goitrogenous areas.

Due to the importance of early detection for CH to

prevent mental retardation, this study was conducted to determine the feasibility of having a CH screening programme at the Maternity Hospital Kuala Lumpur by using cord blood samples.

Methods

After delivery of the foetus and ligation of the umbilical cord, approximately 1 ml to 5 ml of cord blood was withdrawn with a syringe from the placental side of the cord and stored at 4°C.

The blood was then sent to the laboratory where serum was obtained and kept at -20°C until analysis.

Cord serum thyroxine (T4) and thyrotropin hormone (TSH) were measured by radioimmunoassay and immunoradiometric assay respectively using bulk reagents from North East Thames Radioassay, London (NETRIA). Assays were run in singlets and any abnormal results would be repeated. Due to problems with delivery of radioactive tracers, runs of the assay were made at monthly intervals in lots of up to 1,000 samples. With the present preliminary methods, the time interval between the collection of a cord specimen and obtaining the results of the hormone levels varies between 1 to 4 weeks.

Regular sessions with the labour room nurses were held to remind them of the importance of their cooperation for the success of this CH screening study. Mothers were not informed of the study. Cord blood from illegal immigrants was excluded due to the difficulty in obtaining the correct home addresses.

Results

Number of cord blood samples collected

In the one year period from June 1992 to May 1993, 9,402 cord blood samples were collected. This represents only 39% of the total number of deliveries (23,891) at the Maternity Hospital during the studied period.

Cord serum levels of T4 and TSH

Of the 9,402 samples collected, 9,345 samples were assayed for both T4 and TSH and 57 samples assayed

for TSH only due to inadequate amount of cord blood collected.

The mean (\pm S.D) value of cord serum T4 level was 114.97 (\pm 37.6) nmol/L and the data was normally distributed. For TSH log transformation of the data normalised the distribution of cord serum TSH levels. The geometric mean (S.D) was 7.49 mIU/L (1.85) (1-99th centile was 0.23-35 mIU/L).

Table I shows the number of cord samples in relation to T4 and TSH status. TSH was considered high if the value was more than the 99th centile⁴. For T4, the serum level was considered to be low if the value was less than the mean +1 S.D as suggested by the Singapore Congenital Hypothyroidism screening programme⁴. Serum T4 levels less than the mean -2 S.D were also examined.

High TSH was detected in 1.02% of the samples (n=96). Of these, T4 was low (below the mean + 1 S.D) in the majority (n=86) of samples of which in 4 samples, the T4 was below mean -2 S.D. On the other hand, using T4 as parameter, low T4 (less than mean +1 S.D) was present in 88% of samples (n=8,364) of which 98% had normal TSH. The T4 level less than the mean -2 S.D was detected in 0.76% (n=86) of samples of which 94% had normal TSH. There was poor correlation between cord serum T4 and cord serum TSH ($r=0.00746$, $p=0.4715$, $n=9345$). However

Table I
Number (%) of cord samples in relation to T4 and TSH in 9,345 samples

TSH high (> 99 centiles)	n = 96 (1.02%)
T4 > mean +1 SD	= 10
T4 < mean +1 SD	= 86 (0.9%)
	(4 were less than X-2 SD)
T4 low (< mean +1 SD)	n = 8,364 (88.6%)
TSH < 99 centile	= 8278
TSH > 99 centile	= 86
T4 low (< mean -2 SD)	n = 71 (0.76%)
TSH < 35	= 67
TSH > 35	= 4

when samples with TSH > 35 mIU/L were examined, a significant inverse correlation between TSH and T4 was found ($r=-0.31$, $p=0.002$, $n=96$).

Response to recall for retesting

At the beginning of the survey, the first 1,000 samples were analysed for determining the normal range. The TSH was considered to be high if the level was more than the 99th centile which was 33 mIU/L and T4 was considered low if the value was less than 58 nmol/L (derived from mean -2 S.D). All these infants with high cord serum TSH levels ($n=105$) (with high, normal or low T4) were called back for examination and retesting at 1 to 2 months of age. If they did not respond after being called, a second expressed letter would follow. Table II shows the response rate for reexamination.

Of the 50 babies retested, their cord serum TSH ranged from 34-65 mIU/L (median: 40.46). On reexamination, all of them had normal developmental milestones, no goitre and no clinical features of CH. Only 3 babies had TSH levels more than 5 mIU/L with normal T4 (TSH levels were 7.56, 11.23 and 5.77 mIU/L respectively). They are under our close follow up. Of the 4 babies with high TSH and low T4 (less than 2 S.D of the mean), 2 died in the neonatal period, one due to meconium aspiration syndrome and the other due to prematurity with multiple congenital abnormalities. One did not respond to repeated requests for reexamination. A visit to the house address near an animal slaughter area was fruitless as the house had been demolished. The baby failed to be located. The fourth baby was normal and had normal thyroid function on retesting.

Table II
Response to recall for reexamination

Present for retesting	50 (52.1%)
Absent	31 (32.3%)
Neonatal death	4 (4.2%)
Letters returned	11 (11.5%)

Discussion

Even though this study was unable to determine the true incidence of CH at the Maternity Hospital Kuala Lumpur, it was able to identify problems which would help future planning to introduce screening programmes for CH. The major problems identified were poor response to the recall for reexamination, poor cooperation of the staff in the collection of samples and the high recall rate using the criteria set above.

The poor response rate to recall for reexamination was the major reason for the failure of this study to determine the exact incidence of CH. Most of the mothers were not aware and had no knowledge of this condition. Mass education perhaps through the media as well as during antenatal visits may influence the response to recall for reexamination. Another problem which compounded the difficulty in recalling patients compared to the West is the local culture of "transient migration" for delivery or following delivery to their parent's home which could be far from their usual place of residence. During the confinement period of 40 days, the mothers are not permitted to go out, thus preventing them for taking their babies for repeat blood testing. Another problem which was often encountered during the study was incorrect home addresses thus making home visits virtually impossible. This was particularly so among immigrants.

Another major problem was the large number of cord blood samples missing mainly due to the failure of voluntary collaboration of the staff in the labour room in sample collection. The heavy workload in the labour room and lack of staff may explain the situation. The average number of nursing staff during the study period was 17 per day, that was about 6 staff per shift catering for 76-90 deliveries per day. Using a more simple and less time consuming method may probably improve the collection of samples.

A simpler method of sample collection such as filter paper blood spots need to be developed to ease sample collection and transportation. This could be incorporated with the established G6PD screening programme.

Cord blood samples are not the best samples for assessing neonatal thyroid function as the effects of

maternal hormones are highest at this period. The best period for CH screening is at 3-5 days after birth⁵. Newborn CH screening test are usually carried out on dried blood spot samples collected via skin puncture onto filter paper. Either T4 or TSH dried blood spots have been employed successfully for screening purposes. In Malaysia, however, this is not possible as most mother-newborn diads are discharged from the hospital within 1 day of delivery and only occasionally up to 3 days. Home visits by public health nurses usually done within 7 days of delivery covers less than 50% of the total deliveries in Kuala Lumpur. Thus, the best sample to be used in this country for screening of CH is cord blood as has been successfully carried out in Singapore⁵.

In this study of 9,345 cord blood samples, both TSH and total T4 were assayed to reduce the recall rate. We were unable to determine the predictive value for CH of each test as no case of CH was identified. Low T4 less than the mean +1 S.D was detected in 88.5% of which the TSH was normal in the majority. Low T4 less than 2 standard deviation of the mean present in 0.76% of cases, but again in the majority of samples, the TSH was normal. Thus cord blood T4 was not helpful to be used as primary screening test for CH. Furthermore, the correlation between T4 and TSH was poor. In the study by Walfish⁶ comparing the value of cord T4 and capillary blood spot T4 at 4 to 6 days of age, it was found that cord T4 did not correlate well with follow-up blood spot T4. Many maternal factors such as antithyroid medications and hypothyroidism as well as fetal factors such as prematurity and twinning can cause low T4 especially in cord blood samples. This study confirms the findings of others that cord blood T4 is not a good primary screening test for CH. Cord blood TSH is more appropriate as a primary screening test⁷. In Singapore⁵, screening for CH is now routine using

cord blood samples and TSH as the primary test with a supplemental T4 or FT4. Cases with TSH more than the 99th centile and T4 or FT4 below the mean +1 SD are recalled for retesting. The recall rate was 0.7%. In this study, high TSH (more than 99th centile) was identified in 1.02% of the samples. Cases with high TSH and low T4 (less than 2 S.D) were identified in only 0.04%. None of the cases with high TSH and T4 below mean +1 S.D and reexamined were confirmed to have CH. This study therefore suggests that cord blood TSH is a better primary screening test than using cord blood T4. However, we still do not know which is the best cut off level for low T4, probably it can be set at 2 S.D below the mean to reduce the recall rate.

In summary, we have identified the problems which need to be overcome in future plans for screening of CH. A national screening programme incorporating screening techniques, recall and diagnostic criteria can be developed in Malaysia. However, the cost-benefit arguments in planning, starting, funding and maintaining a mass screening programme should be seriously considered.

Acknowledgement

We would like to thank Dato' Dr N. Subramaniam, Senior Consultant & Head Department of Obstetrics and Gynaecology, Hospital Kuala Lumpur, Dr. Gunasegaram and labour room staff of Maternity Hospital Kuala Lumpur for their invaluable cooperation. I would like to thank Messrs Hashim, Alias, Kamaruzaman, Sazali, Miss Jamilah and Norlida for their technical assistance.

This study was sponsored by IRPA Grant 03-07-03-078.

References

1. Delange F, Fisher DA, Glinoe D. Research In Congenital Hypothyroidism, NATO Advanced Science Institute Series, New York: Plenum Press, 1989.
2. Glorieux J, Dussault JH, Morissette J, Desjardins J, Letarte J, Guyda H. Follow-up at ages 5 and 7 years on mental development in children with hypothyroidism detected by Quebec Screening Programme. *J Pediatr* 1986;107 : 913-5.

FEASIBILITY STUDY OF CONGENITAL HYPOTHYROIDISM SCREENING PROGRAMME

3. La Franchi SH, Hanna CE, Krantz PL, Skeels MD, Miyahara RS, Sesser DE. Screening for Congenital Hypothyroidism with specimen collection at two time periods: Results of the Northwest Regional Screening Programme. *J Pediatr* 1985;76 : 734-40.
4. Joseph R, Aw TC, Tan KL. Free thyroxine as a supplement to thyrotropin in cord screening for hypothyroidism. *Ann Acad Med Singapore* 1993;22 : 549-52.
5. Fisher DA. Clinical Review 19: Management of Congenital Hypothyroidism. *J Clin Endocrinol Metab* 1991;72 : 523-9.
6. Walfish PG. Screening for Neonatal Hypothyroidism using Cord Serum T4 Measurements : Comparisons to Neonatal Capillary Dried Blood and Serum T4 Screening Methods. In *Perinatal Thyroid Physiology and Disease*, Raven Press Publishers, 1975 : 249-53.
7. Klein AH, Agustin AV, Foley TP. Successful Laboratory Screening for Congenital Hypothyroidism. *Lancet* 1974;2 : 77-9.