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Congenital Hypothyroid Screening Using Cord Blood TSH

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ABSTRACT

Background: Clinical diagnosis of congenital hypothyroidism (CH) is difficult at birth without neonatal screening. In line with the priorities of the national health services in Malaysia towards preventive medicine, early diagnosis and treatment of CH is emphasised. We conducted a pilot study at Kuala Lumpur's Maternity Hospital between April 1995 and November 1995 to estimate the incidence of CH and also evaluated the problems associated with large-scale neonatal screening using a commercial TSH kit on cord bloodspots.

Patients: A total of 11,000 newborns were screened using cord bloodspots taken at birth.

Results: Two hundred and fifty newborns (2.27%) had cord TSH > 20 mIU/L and had to be recalled for re-evaluation. Of these, 4 had cord TSH of > 100 mIU/L; three were confirmed to have congenital hypothyroidism and one had transient hyperthyrotropinaemia. Our study estimated the incidence of CH to be one in 3,666 live births in Kuala Lumpur, Malaysia. Clinical features of hypothyroidism are subtle during the early weeks of life. However, prolonged neonatal jaundice (3/3), widely opened posterior fontanelle (3/3) and dry skin (3/3) were the common features in all our cases by 2 – 6 weeks of life.

Conclusion: This study suffered a high dropout rate. Twenty-six percent of the patients were not traceable after discharge and 48% did not respond to our recall. We stress the importance of public education and awareness in contributing to the cost-effectiveness of the screening program.

Keywords: congenital hypothyroidism, neonatal screening, cord blood TSH

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INTRODUCTION

Congenital hypothyroidism is the most common preventable cause of mental retardation in children. Clinical features are often lacking at birth even up to the first few weeks or months of life. Diagnosis based on clinical features is difficult at birth without biochemical screening resulting in delayed initiation of therapy and irreversible brain damage in the affected children. Retrospective clinical studies showed that less than half were diagnosed by three months and approximately two-thirds by one year of age[1,2]. Since the introduction of routine neonatal screening over the past two decades, the incidence of congenital hypothyroidism has proven to be considerably higher than before. Incidence based on clinical diagnosis had been found to vary between one in 5,800 and one in 6,900[1-5], whereas for those which were based on neonatal screening, the incidence was between one in 2,900 and one in 3,600[6,7]. There had been suggestions about its higher incidence among premature infants[8], the Asian population[9,10], increased morbidity and mortality[11] and an increase in associated congenital abnormalities[12] including chromosomal abnormalities[13]. Early diagnosis and adequate treatment of congenital hypothyroidism before the clinical manifestations have shown to protect against brain damage manifested by lowered IQ scores[14-21].

In Malaysia, we have an annual birth rate of approximately 550,000[22]. Based on the general incidence, we estimate at least 100 babies to be born with congenital hypothyroidism each year. This poses a potential health problem and burden to the family and the nation at large. Yet, CH screening is not routinely done due to many logistical constraints: 1) shortage of staff to supervise the collection and transport of blood samples; 2) difficulty and unreliability of transportation system. Hence sample losses, tube breakages and late arrival of samples to the laboratory are not uncommon; 3) lack of adequate laboratory facilities to cope with large number of tests. Blood/serum samples often have to be transported from distant or remote areas to the central laboratory for assay; 4) rapid population migration and movement especially in the towns and cities, make difficult recalling of the patient when the time arises; 5) untraceable addresses of many squatter population and 6) the general public's lack of knowledge and awareness of CH and its consequences, result in poor patient co-operation. Despite the above setbacks, Malaysia enjoys a good infrastructure of healthcare system which extends to reach the most remote part of the rural areas. Up to 90% of all our deliveries are now being conducted by trained personnel. Moreover in Malaysia, we have an existing neonatal screening programme for G6PD deficiency using cord blood on filter paper. It will be advantageous for the CH screening to tag onto this existing screening programme.

In line with the priorities of health care services in Malaysia towards preventive medicine, early diagnosis and treatment of CH is emphasised. We conducted a

pilot study in Kuala Lumpur's Maternity Hospital between April 1995 and November 1995 to estimate the incidence of CH, and to evaluate the problems associated with its large scale neonatal screening using a commercial TSH kit on cord bloodspots taken at delivery.

METHOD

The Maternity Hospital, Kuala Lumpur has an annual birth rate of 28,000. It serves mainly the population of Kuala Lumpur, the capital city of Malaysia. During registration for admission to the hospital, all parents-to-be were given a write-up about the current study, stating its purpose and importance in three languages (English, Malay, Mandarin). Parents-to-be were also requested to provide their current addresses and telephone numbers if these were different from what were written on their antenatal hospital records. At delivery, cord blood was collected on filter paper, which was the size of a 50-cent coin. This was left to dry and kept at room temperature until it was transported to the laboratory on the same day. Delivery of the dried bloodspots to the laboratory was done twice.

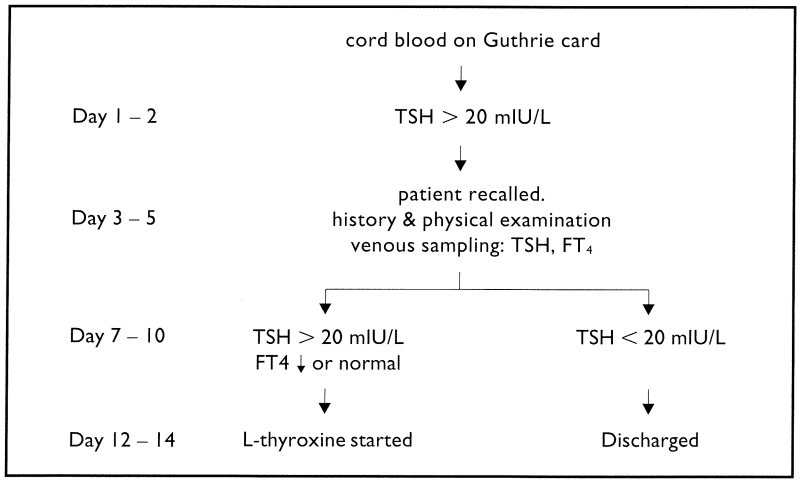

Fig 1 – Neonatal hypothyroid screening in Maternity Hospital, Kuala Lumpur

Table I – Results of congenital hypothyroid screening

Number of newborns screened	11,000
Median cord TSH	4.83 mIU/L
Range of cord TSH	0.5 – 77.5 mIU/L
TSH > 20 mIU/L	250
Recall rate	2.27%
Confirmed hypothyroidism	3

Table II – Distribution of filter paper cord blood TSH

Cordblood TSH (mIU/L)	No. of patients	No. of patients who responded to recall	Confirmed hypothyroid
20 – 40	204	52 (25.5%)	0
40 – 60	37	8 (21.6%)	0
60 – 80	5	1 (20.0%)	0
> 80	4	4 (100%)	3
Total	250	65 (26%)	3

At the laboratory, a 1/4 inch disc was punched out from the bloodspot, and the serum eluted using eluting buffer. TSH was assayed using a commercial kit (Immuchem Neonatal TSH-MW Elisa, ICN Diagnostic). Results were available within six hours. Babies who had TSH levels more than 20 mIU/L had their hospital records retrieved and were recalled to the endocrine clinic via phone, letters or personal home visits, based on updated information given at admission. These babies were examined by the paediatric endocrinologist for features of hypothyroidism, and venous blood was taken for free T_4 and TSH screening, (using the established method (TSH-IEMA Elisa kit, Netria) to confirm the diagnosis. Babies were confirmed to have congenital hypothyroidism if their free T_4 was low or normal with persistently high TSH level > 20 mIU/L. For these patients, treatment with L-thyroxine was started immediately and were monitored closely (Fig 1).

RESULTS

Eleven thousand newborn babies were screened during this period (Table I). The median level of cord blood TSH was 4.83 mIU/L, with a range of 0.5 to 77.5 mIU/L. There were altogether 250 babies who had cord TSH > 20 mIU/L. This gave a recall rate of 2.27%. Amongst these babies, 204 babies (81.6%) had TSH between 20 – 40 mIU/L, 37 (14.8%) had TSH between 40 – 60 mIU/L, 5 (2.0%) between 60 – 80 mIU/L, and 4 (1.6%) had TSH more than 80 mIU/L (Table II). However, only 65 (26%) babies responded to the recall for further evaluation and confirmation of their hypothyroid state. Sixty-six (26%) babies were not traceable due to improper or incomplete addresses. Some were invalid addresses, while the rest were no longer at the addresses given. In 119 (48%) cases, the addresses were traced and the parents informed via phone, letters or home visits. Despite the efforts by the hospital staff, some parents had refused to take their babies for re-evaluation (Fig 2). This was attributed to the general lack of knowledge/information about the illness and its consequences, parental indifferent attitude, denial or even fear of acceptance of the illness and its social stigma. Nevertheless, all the four babies who had cord blood TSH > 80 mIU/L returned for evaluation because of the persistent effort of the team. All four of them had very high cord blood TSH (above 100 mIU/L) (Table III), and on re-evaluation, the TSH escalated even higher in three of them and was associated with a low free T_4. They were confirmed to have CH and thyroxin was started immediately. In one baby who had initial cord TSH > 100 mIU/L, the TSH declined markedly to 26 mIU/L on re-evaluation (day 15), and normalised by day 23. This baby had transient hyperthyrotropinaemia but did not require treatment. On subsequent follow-up at six months of age, the baby was well, with normal developmental milestones. Among 10 babies with cord TSH 20 – 80 mIU/L, their TSH levels normalised on re-evaluation, and all of them had normal free T_4 levels.

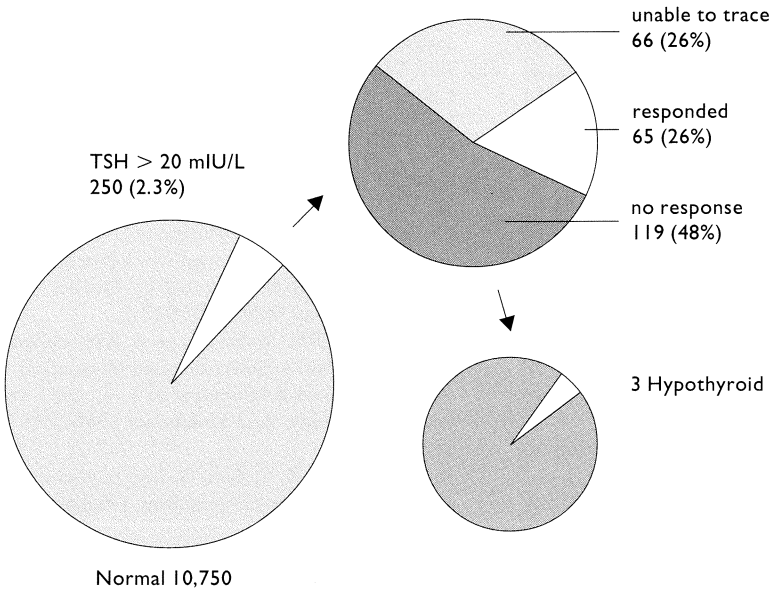

Fig 2 – Neonatal hypothyroid screening in Maternity Hospital Kuala Lumpur
Samples assayed 11,000 newborns

Table III – High TSH on screening

Patient	Cordblood TSH (mIU/L)	Confirmatory tests TSH (mIU/L)	FT_4 (pmol/L)	Age (days)	Treatment started (days)
C1 (Malay)	215	454	2.1	Day 14	Day 15
C2 (Malay)	455	559	5.1	Day 21	Day 22
C3 (Indian)	164	26.9	19.8	Day 15	-
C4 (Malay)	111	283	16.3	Day 10	Day 13

Table IV – Neonatal hypothyroid screening – racial distribution

Malays	61.0%
Chinese	14.6%
Indians	12.4%
Indonesians	9.8%
Orang Asli	1.7%
Others	0.5%

Table V – Characteristics of hypothyroid patients

	Case 1	Case 2	Case 3
Parental consanguinity	nil	nil	nil
Family history	nil	nil	nil
Gestation	term	term	term
Adverse perinatal events	nil	nil	nil
Sex	female	female	male
Birth weight (kg)	3.60	3.51	2.97
Lethargy	nil	nil	nil
Feeding/breathing difficulty	nil	nil	nil
Prolonged jaundice	yes	yes	yes
Constipation	nil	mild	nil
Dry skin	yes	yes	yes
Posterior fontanelle (cm)	> 0.5	> 0.5	> 0.5
Hypothyroid facies	nil	nil	nil

All the affected babies were Malays. However, this may not represent racial predilection because of the small number of patients and moreover, the majority of the babies screened here were Malays compared to other races (Table IV). Amongst the three hypothyroid babies, there were no obvious risk factors which included prematurity, low birth weight, adverse perinatal events, family history or parental consanguinity. However, two of the three cases were females and this was comparable with the finding of female predominance shown in other studies. Again, we have to take into consideration the small sample size. Features of hypothyroidism were minimal in the early weeks of life. All the three cases had prolonged neonatal jaundice of indirect hyperbilirubin type. The jaundice was mild except for one who required phototherapy for two days. One of them had relative constipation, with bowel opening once in two days despite being breastfed totally. All three of them had some degree of dry skin, and widely opened posterior fontannelle. Hypothyroid facies was not seen in any one of them.

DISCUSSION

Two screening methods have been used for congenital hypothyroidism[23-26]. A primary T_4 screening or TSH screening. T_4 screening alone however has low specificity, misses hypothyroid cases with normal T_4, but high TSH. It includes false positives of hypothyroxinaemia among the premature neonates. To minimise these problems, a higher cut-off T_4 value carefully selected with supplemented TSH is preferred. This however increases the recall rate and the cost of screening. A sensitive primary TSH screening would be a more specific index of abnormality as primary hypothyroidism accounts for more than 90% of all cases. However, this method misses hypothalamic-pituitary hypothyroidism which is not common, occurring in 1 out of 50,000 to 100,000 live births. Cases of delayed rise in TSH after birth would be missed by this screening. However, this is a rare occurrence. False positives include transient hyperthyrotropinaemia which is an uncommon event, and does not require treatment.

Neonatal hypothyroid screening using cord blood on filter paper is an easy, practical and effective method. The estimated incidence of congenital hypothyroidism in Kuala Lumpur is 1 in 3,666 livebirths based on our study. This is comparable with incidence in the developed countries. Affected children in our study had cord blood TSH level above 100 mIU/L which is well above the median level. One child had transient hyperthyrotropinaemia which normalised by the 23rd day of life. Poor public awareness of the illness and its consequences as well as incorrect addresses were the major setbacks in our study which resulted in a poor recall rate.

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