

NEWBORN SCREENING IN INDONESIA

Diet S Rustama, M Ryadi Fadil, Elly R Harahap, Aris Primadi

Department of Child Health and Department of Nuclear Medicine, Padjadjaran University School of Medicine, Hasan Sadikin General Hospital, Bandung, Indonesia

Abstract. In Indonesia, newborn screening is not yet a policy, and the incidence of preventable causes of mental retardation detected by newborn screening is not known. Congenital hypothyroidism (CH) is not infrequent. Without a screening program, unrecognized CH patients were neglected for years. Since May 1999, the International Atomic Energy Agency (IAEA) has assisted in starting a CH Newborn Screening Project to estimate the local incidence of CH and to evaluate the problems associated with the screening. In June 2000, a pilot study was conducted using primary TSH measurement, supplemented by T_4 in infants with elevated TSH. The target was to screen 12,000 newborn infants, using cord blood serum taken at birth, or a heel prick between 2 to 6 days of age. Between June 2000 and February 2001, 3,534 neonates born in 4 hospitals were screened using cord blood serum taken at birth (recall rate 3.3%). From March 2001 onwards, the heel prick method was used and participating hospitals increased from 4 to 7. Using this approach, until August 2001, 3,309 samples were analysed and the recall rate was much lower (0.64%). The number of unsatisfactory samples was relatively high due to an unstable process of blood collection. Parental refusal and low acceptance of screening among policy makers resulted from lack of awareness of the dangers of CH, and the screening program was not considered a health priority. Recall of patients after screening was a major barrier, with problems in tracking patients arising from urbanization and a high rate of relocation. To advance the CH screening program nationwide, infrastructure must be improved along with the recall system, and education as well as information campaigns for parents and medical professionals must be intensified. The Department of Health must be persuaded to give a national mandate.

INTRODUCTION

Newborn screening is a preventive public health program that should be available to all neonates (Last *et al*, 1992). In developed countries, this has already been a routine procedure for years. Among Southeast Asian countries, the first report was from Singapore, when screening for congenital hypothyroidism was conducted in 1981 (Yeo *et al*, 1982). In the beginning of the nineties, Korea, Malaysia and Thailand started the pilot study. In the Philippines, a newborn screening project was started in 1996. Overall incidence of congenital hypothyroidism (CH) in East Asia is approximately 1: 3459 (Therrell, 1999). In Indonesia, communicable diseases, infection and malnutrition remain the leading causes of morbidity and mortality. The priorities of the government policies are to reduce these conditions, therefore it is extremely difficult to justify newborn screening programs from the government's point of view (Indonesia's Health Profile, 1998).

Among preventable causes of mental retardation detected by newborn screening, congenital hypothyroidism is the most common, while other causes such as phenylketonuria are more rare. It might be possible that endemic congenital hypothyroidism is more prevalent

in Indonesia, as there are still many areas of iodine deficiency scattered around the country. An estimated 42 million people live in these areas (Azwar, 2000). A local study in an iodine deficient district in Central Java showed an incidence of 1: 1500 for permanent CH and 1: 300 for transient CH (Sunartini *et al*, 1999). Thus, there are likely large numbers of undetected cases in iodine deficient areas. Even though the disease is temporary, the impact on the developing brain would impair the quality of mental capacity in the same way as sporadic congenital hypothyroidism.

The early diagnosis and treatment of CH are vital for therapeutic success, but to make the diagnosis in the early days of life is very difficult because of the absence of clinical signs at that age (Alm *et al*, 1978). Without a screening program in Indonesia, most CH patients were diagnosed late. They were unrecognized cases of CH for years, consequently neglected, and missed their chance for a normal life. Treatment with thyroid hormone restored their physical growth close to normal within a couple of years, but their mental development remain very disappointing (Sutan, 1985; Rustama, 1998). Screening for CH in all newborns provides a solution. Nevertheless, the implementation of a neonatal screening program in a developing country like Indonesia presents

many problems. The International Atomic Energy Agency (IAEA), has assisted in introducing a screening system for congenital hypothyroidism and to reduce the prevalence of mental retardation within the region.

The purpose of this study is to estimate a local incidence of congenital hypothyroidism and also to identify and evaluate various obstacles that may be faced during the screening process.

MATERIALS AND METHODS

Patients were neonates born in 5 general hospitals and 2 maternity hospitals. In July 2000, a pilot study was begun with 4 participating hospitals. The prevalence study is ongoing and the target is to screen 12,000 neonates. TSH was used for primary screening, with plasma TSH and T₄ measurements being used as confirmatory tests for samples having high TSH results. The kits used (Skybio LTD, UK) were double antibody radioimmunoassay for TSH and coated-tube radioimmunoassay for T₄. At the beginning of the study (from June 2000 until March 2001) cord blood taken at the birth location was used and from March 2001

onwards, dried blood specimens from heel-pricks taken between 2 and 6 days of age were used. Blood samples were applied to 3/16 inch circles on filter paper cards (903c obtained from Schleicher and Schuell, Keene, New Hampshire, USA).

Infants with elevated and borderline TSH values were recalled for serum T₄ and TSH tests. Clinical assessment for features of congenital hypothyroidism (congenital hypothyroid index) and for other congenital malformation was also done. Infants with a low T₄ level and a TSH concentration greater than 50 µU/ml, was considered to have primary hypothyroidism until proven otherwise. Detected CH cases were treated with an initial dose of 10-15 µg/kg of weight per day (American Academy of Pediatrics, 1993).

RESULTS

A total of 6850 samples (3541 cord blood and 3309 heel sticks) were obtained. Fifty-three could not be analyzed. Table 1 summarizes the data. All unsatisfactory samples should have been recollected, but only 11 of 53 (20.75%) could be recruited for another

Table 1. Summary results.

Screening approach	No. infants screened	Unsatisfactory samples	Positive samples (recall rate)	Diagnosed case on T _x	Days from birth to diagnosis	Cases missed
Cord blood serum	3534	7	116	(3.28%)	1	21
Dried blood spot	3263	46	21	(0.64%)	-	-
Total	6797	53 (0.78%)	137 (2.02%)	1	21	

Table 2. Cord blood serum TSH measurements.

TSH concentration (µU/ml)	No. infants screened	Percentage
<25	3418	96.72
25-50	112	3.17
>50	4	0.11
Total	3534	100.00

Table 3. Filter paper blood spots TSH measurements.

TSH concentration ($\mu\text{U/ml}$)	No. of infants screened	Percentage
<20	3242	99.36
20-50	17	0.52
>50	4	0.12
Total	3263	100.00

test. Positive testing results were: TSH concentration of $>25 \mu\text{U/ml}$ for cord serum, and $> 20\mu\text{U/mL}$ for dried blood spots. Positive results were obtained on 116 of 3,534 cord blood tests (recall rate of 3.28%) (See Table 2) and 21 of 3,242 heel stick samples (recall rate of 0.64%) (See Table 3). Most patients with positive results did not have confirmatory tests due to problems in tracking their addresses.

One detected infant was diagnosed as having thyroid agenesis on the basis of thyroid scanning. He had a markedly elevated TSH value ($115.8 \mu\text{U/ml}$), and a low T_4 concentration (3.82 ng/dl). He was started on thyroid replacement therapy at 21 days of age. This patient had several features of congenital hypothyroidism: jaundice for more than three weeks, umbilical hernia, macroglossia, and constipation. An infant with Down Syndrome presented with low T_4 (6.5 ng/dl) and slightly elevated TSH ($7.1 \mu\text{U/ml}$) on the first confirmatory test and several follow-up tests were essentially the same. TSH and T_4 values at 6 months of age were $13.2 \mu\text{U/ml}$ and 5.6 ng/dl respectively. Whether this infant needs treatment has not yet been determined. Two of the recalled samples showed low T_4 but normal TSH (TSH $3.72 \mu\text{U/ml}$, T_4 4.7 ng/dl and TSH $2.4 \mu\text{U/ml}$, T_4 5.6 ng/dl).

DISCUSSION

Newborn screening aims to detect primary congenital hypothyroidism, permanent or transient. This may be accomplished by measuring TSH in filter paper blood spots or cord serum or by measuring thyroxine supplemented by TSH when T_4 values are relatively low (Fisher, 1983). Screening using TSH constitutes a sensitive index for detecting primary hypothyroidism, but secondary hypothyroidism and primary hypothyroidism with a delayed rise in TSH are missed (Dussault *et al*, 1976).

The study began with cord blood samples since cord blood sampling was considered to be simple, non-invasive

and did not require collection training (Amar, 1997) because most births in the village are assisted by a midwife and a non-health professional. However, screening with this method resulted in a very high recall rate and therefore, the sample collection method was switched to heel prick. The heel stick method can also be extended to screen other metabolic diseases such as phenylketonuria (PKU) while cord blood cannot.

The acceptable recall rate for primary TSH screening is approximately 0.05% (American Academy of Pediatrics, 1993). In this study, the recall rate for filter paper spot TSH measurement was relatively high and may have been caused by imprecise sample collection. Some of the recalled samples showed low T_4 but normal TSH values, indicating possible TBG deficiency, hypothalamic immaturity, hypothalamic pituitary hypothyroidism or primary hypothyroidism with delayed TSH elevation. Further follow-up for these was not attempted. The infant with Down Syndrome had borderline results on the first and subsequent screening and confirmatory tests and illustrated the difficulty in achieving a proper diagnosis in cases of Down Syndrome (Daliva *et al*, 2000).

CONCLUSIONS AND RECOMMENDATIONS

Accurate screening results depend on good quality of blood spots. As many as 0.78% of filter paper spot samples were not analyzed due to imprecise drops of blood or failure to fill or overflow the designated area. This suggests that taking blood or sample collection still must be constantly supervised. Moreover, only a few patients returned for blood testing because of unsatisfactory samples.

The return of recalled patients to replace unsatisfactory samples or for confirmatory T_4 and TSH measurements is a major problem. Tracking the address, many of which were incorrect or no longer valid, is difficult since families frequently move from one location to another with no forwarding addresses. To overcome this

problem, improved infrastructure is needed, such as issuance of identity cards for all citizens, and government cards for recording newborn screening results in the same way as immunization records. Involvement of policy makers at all levels is required for this to occur.

Missed cases could not be easily identified, as there is no report system for affected infants missed by the program. Fisher in 1987 described the likelihood of missed cases, even with the successful newborn screening programs. Sixty-three percent of the Indonesian population live in the village, most of them remote and lacking easy access resulting in major barriers to communication of results and recall. Socio-cultural influences are widely different among various ethnic groups, and resistance is likely from the parents for an invasive test to be performed on their apparently normal looking infants.

It is clear that true incidence rates cannot yet be determined in this program. To advance the CH screening program nationwide, infrastructure must improve, the recall system must be aggressive, education and information campaigns for parents and medical professionals must be intensified, and the Department of Health must be persuaded to give a national mandate. The pilot study is ongoing and the problems observed are valuable for improving the program.

ACKNOWLEDGEMENTS

This study has been supported by The International Atomic Energy Agency (IAEA), funded in part by PT BIOFARMA, and in part by free-will donations by participants. We also acknowledge the support and advice of Professor Johan S. Masjhur, Head of The University Research Centre and The Department of Nuclear Medicine; Dr Suganda Tanuwidjaja, the Head of The Department of Child Health, School of Medicine, Padjadjaran University Hasan Sadikin General Hospital. We thank all members of The Newborn Screening Working Group West Java Province, all participating hospitals and laboratory staff for their cooperation.

REFERENCES

Alm J, Larson A, Zetterstrom IR. Congenital hypothyroidism in Sweden. Incidence and age at diagnosis. *Acta Paediatr Scand* 1978;67:1-3.

- Amar HSS. Screening for congenital hypothyroidism in Southeast Asia. *J Paediatr Obstet Gynaecol* 1997; Jan/Feb:1-6.
- American Academy of Pediatrics: Section on Endocrinology and Committee on Genetics, and American Thyroid Association Committee on Public Health. Newborn Screening for Congenital Hypothyroidism. *Pediatrics* 1993; 1:1203-9.
- Azwar A. IDD Control Program in Indonesia. Presented at The 5th National Congress of Indonesian Society of Endocrinology. Bandung 9 April, 2000.
- Daliva AL, Linden B, DiMartino-Nardi J, and Saenger P. Three-year follow up of borderline congenital hypothyroidism. *J Pediatr* 2000;136:53-6.
- Dussault JH, Parlow WF, Letarte J, Guyda H, Laberge C. TSH measurement from blood spot on filter paper: a confirmatory screening test for neonatal hypothyroidism. *J Pediatr* 1976;89:550-2.
- Fisher DA. Effectiveness of newborn screening programs for congenital hypothyroidism: prevalence of missed cases. *Pediatr Clin North Am* 1987; 34:881-90.
- Fisher DA. Second International Conference on Neonatal Thyroid Screening : Progress Report. *J Pediatr* 1983; 653-4.
- Indonesia's Health Profile. Department of Health. Government of Indonesia, 1998.
- Last JM, Wallace RB, eds. Public Health & Preventive Medicine. 13th ed. Norwalk, Connecticut : Appleton & Lange, 1992.
- Rustama DS. Thyroid hormone on growth and development. Bandung: Clinical Endocrinology II Symposia. Endocrine Study Group, 1998.
- Sunartini, Tokumi T, Nakajima T, *et al.* Screening of thyroid function in endemic iodine deficiency disorder areas in Yogyakarta [Abstract]. Bangkok: The Asian Federation of Endocrine Society, 1999.
- Sutan, Assin M. Congenital hypothyroidism [Abstract]. New Delhi, India; The World Congress of the International Association for the Scientific Study of Mental Deficiency, March 24-28, 1985.
- Therrell B. Proceedings of a Workshop on National Neonatal Screening for Congenital Hypothyroidism in East Asia. Seoul-Korea, 17-21 May, 1999.
- Yeo PPB, Joseph R, Chng KP, *et al.* Screening programme for congenital hypothyroidism in Singapore. Proceeding of 2nd International Conference on neonatal thyroid screening. Tokyo, August 1982; 113-4.