Five-Year Thyrotropin Screening for Congenital Hypothyroidism in Ramathibodi Hospital

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Abstract

Objectives : To detect newborns with congenital hypothyroidism (CH) and to treat the affected infants as early as possible.

Study design : Cord blood thyrotropin (TSH) screening for CH in Ramathibodi Hospital began in 1993. From October 1993 to December 1998, 35,390 neonates were screened. The infants with elevated TSH level of greater than 30 mU/L were recalled for verification of CH. Confirmation tests included total thyroxine, free thyroxine and TSH level. Thyroid scan and uptake were performed in some affected infants.

Results : Twelve infants with CH were detected resulting in an incidence of one in 2,949 live-births. All affected infants were asymptomatic at birth. Of 12 infants with CH, one premature neonate had a delayed TSH elevation and was diagnosed as having primary hypothyroidism at 2 months of age.

The recall rate for validation of CH based on a cut-off value at serum TSH level of greater than 30 mU/L is 1.1 per cent. If the cut-off value of serum TSH level was raised to greater than 40 mU/L, the recall rate would decrease to 0.43 per cent. None of the affected infants had cord blood TSH level of less than 50 mU/L except one premature patient. Therefore, beginning in January 1997, the cut-off value of TSH was raised to 40 mU/L or greater.

Pitfalls in this program include incomplete blood-specimen collection and incomplete follow-up. To strengthen the program, improvements were made in the follow-up system from 1996 onward. Therefore, the coverage for blood-specimen collection progressively increased from 84 per cent in 1994 to 96 per cent in 1998. Simultaneously, the patients' return after recalls also increased from 38 per cent to 100 per cent.

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Conclusions : The incidence of CH in Ramathibodi Hospital is approximately 1:3,000 live-births. The optimal cord blood TSH level for recall is 40 mU/L or greater. The intensification of follow-up strategy resulted in better response to recall and earlier treatment in the affected infants.

Key word : Thyrotropin Screening, Congenital Hypothyroidism, Five-Year at Ramathibodi Hospital

Congenital hypothyroidism (CH) causes irreversible brain damage resulting in mental retardation[1]. Because the symptoms of hypothyroidism during neonatal and infancy period are scanty and nonspecific, and treatment of CH before 1 month of age improves mental function[1]. Therefore, screening program for CH in neonates is necessary to detect affected infants as early as possible.

Screening program for CH in Ramathibodi Hospital was initiated in 1990. Rajatanavin et al[2] reported the 1-year pilot study on screening for CH in Ramathibodi Hospital and demonstrated that the program was cost-benefit. The worldwide incidence of CH is approximately 1:4,000 live-births with a range from 1:2,000 to 1:7,000 live-births[3-5]. The incidence of CH was much greater in the areas of iodine deficiency[6].

In Thailand, the first report from southern Thailand in 1986 by Sukthomya et al demonstrated the incidence of approximately 1:4,000 live-births [7]. Since 1990, screening programs for CH were conducted in many parts of the country. The studies from Bangkok which was previously demonstrated to be marginally iodine-deficient area revealed the incidence of CH was 1:2,500[2]. Recent study in our laboratory during 1996-1997 in Bangkok revealed median urine iodine of 10.5 μg/dl which indicates adequate iodine status in this population. This data suggests the effectiveness of the national campaign of using iodized salt and the declaration of iodization law during the past 5 years. Recent report by Thaithumyanon et al at Chulalongkorn Hospital, Bangkok revealed the incidence of CH was 1:4,000 live-births[8]. In contrast, the studies from endemic areas of iodine deficiency demonstrated the higher incidence ranging from 1:600 to 1:1,200 live-births [9-11]. Moreover, high incidence of endemic cretinism in northern Thailand was reported[12].

In Ramathibodi Hospital, the pilot study on newborn thyroid screening program was initiated by measuring thyrotropin (TSH) in umbilical cord serum specimens in 1990[2]. After this pilot study, this program became a routine service. This study presents the experience on five-year thyroid screening program in Ramathibodi Hospital. The pitfalls of the program as well as strategy of solving the problems are presented.

SUBJECTS AND METHOD

The study was conducted at Ramathibodi Hospital from October 1993 to December 1998. All neonates born in the labor room and operating room were screened by collecting cord blood at birth. The specimens were sent to a central laboratory for assay of serum TSH levels. Serum TSH assays were performed on a daily basis. Neonates who had serum TSH concentration of greater than 30 mU/L were recalled immediately by mail. Since 1996, the follow-up system has been improved by having one person responsible for recall the patients by phone, mail and/or home visit. In addition, the cut-off value of TSH has been raised to 40 mU/L since 1997. Infants with elevated TSH levels were thoroughly examined for symptoms and signs of hypothyroidism. Venous blood samples were collected for thyroid function tests (TFTs) which included free thyroxine (FT_4), total thyroxine (T_4) and TSH levels. If TFTs confirmed the diagnosis of CH, thyroid scan and uptake were performed to determine the etiology of CH. The neonates with confirmed CH were immediately put on levothyroxine ($L\text{-}T_4$) replacement therapy. Long-term treatment and follow-up have been performed in the Pediatric Endocrine Unit.

Serum TSH concentration was determined by immunoradiometric assay using commercial kits

Table 1. Coverage of TSH screening in Ramathibodi Hospital from October 1993 to December 1998.

Year	Total births	No. screened	%
1993	1,702	1,602	94.1
1994	7,738	6,530	84.4
1995	7,725	6,218	80.5
1996	7,650	6,918	90.4
1997	7,658	7,380	96.4
1998	7,069	6,742	95.4
63 mo.	39,542	35,390	89.5

(Serono, Switzerland) during 1993-1995 and enzyme-linked immunosorbent assay (DPC, U.S.A.) during 1996-1998, serum T_4 by chemiluminescence assay (DPC, U.S.A.) and serum FT_4 by radioimmunoassay (DPC, U.S.A.).

RESULTS

From October 1993 to December 1998, 35,390 neonates were screened for CH. The average coverage of thyroid screening was 89.5 per cent. Significantly, the coverage increased to greater than 95 per cent in the last 2 years as shown in Table 1. The main problem was incomplete blood specimens collection.

Infants with elevated TSH level of greater than 30 mU/L were recalled for validation of CH. By using this cut-off value, the recall rate ranged from 0.56 per cent to 1.94 per cent. During the 3 years period of screening, all newborns with the cord serum TSH levels between 30 and 40 mU/L had been confirmed euthyroid by demonstration of normal TFTs. Moreover, there were no documented late-onset congenital hypothyroidism in this group. Hence, in 1997, the cut-off value of TSH was raised to 40 mU/L, resulting in the recall rate of 0.42-0.43 per cent (Table 2). If the incidence of CH is 1: 3,000-1:4,000 live-births, this means that approximately 10-15 infants may be recalled for TFTs for every one case of CH.

The percentage of neonates' return for TFTs is shown in Table 2. During the first 3 years (1993-1995) of the program, newborns were recalled by mail only. The follow-up system was unsatisfied as shown by the very low response rate ranging from 3.2 per cent to 37.9 per cent. Since 1996, the follow-up system has been improved by having one person assigned to recall the patients by phone, mail and/or home visit. This person was also responsible for making an appointment for infants with elevated TSH level to be seen by pediatricians. To confirm the diagnosis, blood was obtained for TFTs. The results were reported to the pediatric endocrinologist. Then, the parents were informed about the results of TFTs. Since 1997, the cut-off value of TSH has been raised to 40 mU/L. Therefore, for the last 2 years (1997-1998), the follow-up system has been completely achieved (100%).

Of 35,390 neonates screened for CH, 12 patients with CH were found (Table 3). One patient died of chromosome abnormality and one has never returned for TFTs due to changed address. One preterm (No. 10) was missed by screening due to delayed TSH elevation. This patient presented with growth retardation and constipation and was diagnosed as having CH at 2 months of age. Patients No. 8 and No. 9 had transient hypothyroidism due to maternal anti-thyroid drug. The median age at diagnosis was 17 days (range 5-46 days).

Table 2. Recall rate and return rate in infants with elevated cord serum TSH.

Year	No. screened	TSH > 30 mU/L	Recall rate (%)	Return rate for repeated test (%)
1993	1,602	31	1.94	3.2
1994	6,530	87	1.33	37.9
1995	6,218	35	0.56	31.4
1996	6,918	88	1.27	68.2
1997	7,380	71 (30)*	1.00 (0.42)*	100.0
1998	6,742	69 (29)*	1.02 (0.43)*	100.0
Total	35,390	381	1.08	-

*Recall for TFTs when TSH ≥ 40 mU/L

Table 3. Thyroid function tests in 12 patients with CH diagnosed by TSH screening.

No.	Cord TSH (mU/L)	Cord T_4 (μg/dl)	T_4 (μg/dl)	FT_4 (ng/dl)	TSH (mU/L)
1	592	-	2	0.3	1,063
2	144	-	8.5	1.3	14.3
3	97.4	-		(died, chromosomal abnormality)	
4	85	-		(not return)	
5	712	3.8	0	0	> 118
6	258	6.3	4.7	0.2	> 50
7	400	4.2	0.5	< 0.15	> 50
8	>87	7.6	9.7	1.0	84.7
9	>50	7.6	6.4	0.7	67.7
10	7.6	-	1.1	0.02	> 50
11	>50	2.4	3.1	0.6	QNS*
12	>100	-	6.1	0.5	> 50

*QNS = quantity not sufficient

DISCUSSION

To detect CH, there are several screening procedures which include T_4 alone, TSH alone, T_4 and supplemental TSH, and T_4 plus TSH. Screening by T_4 alone gives the lowest sensitivity whereas the latter 3 procedures give similar incidences of CH[5].

The reason for using cord blood TSH screening in this study was threefold. First, it is convenient to obtain cord blood which can be used either serum or blood spot on filter paper for TSH assays. However, it is not suitable for phenylketonuria (PKU) screening. Second, for screening both CH and PKU, optimal time for specimen collection is 3-7 days after birth. Presently, because of early discharge home, early specimen collection will increase the false positive rate which is due to TSH surge during the first 48 hours of life. Therefore, by using cord blood, it is not necessary for infants to stay in hospital for 2-3 additional days. Third, district hospitals in Thailand are equipped with instruments for preparing and saving serum samples before transportation. Therefore, cord blood is feasible and suitable for thyroid screening in Thailand.

The incidence of CH surveyed in this study was 1:2,949 live-births which is slightly higher than that of worldwide of 1:4,000. If one patient who has not returned for confirmation of CH (No. 4, TSH = 85) and one with early neonatal death due to chromosomal abnormality (No. 3, TSH = 97.4) were excluded, the incidence would be 1:3,539 live-births. One premature neonate out of 12 affected infants with CH was missed by this screening program. This may be due to immaturity of pituitary-thyroid axis in prematurity resulting in delayed TSH elevation. Therefore, some infants with mild or unusual forms of CH will go undetected regardless of the completeness of the screening program. Hence, physicians caring for infants must not depend solely on screening to detect all cases, rather they must continue having high index of suspicion in cases presenting with minimal signs and symptoms of CH.

TSH level in newborn is dependent upon method of TSH assay, environmental iodine and age of infants when blood is obtained. Therefore, most screening programs initially encountered a problem of determining the optimal cut-off value of TSH which varied from 20 mU/L to greater than 50 mU/L[5]. The incidences of transient hyperthyrotropinemia with normal T_4 and transient primary hypothyroidism are higher in iodine deficient areas comparing to those of iodine-sufficient areas[13]. Hence, this cut-off value used in different centers should be different. Initially, the cut-off value of 30 mU/L was used, resulting in the recall rate of about 1 per cent. This recall rate is quite high because about 30-40 infants have to be recalled for every one case of CH. The optimal recall rate based upon incidence of CH of 1:2,500 to 1:4,000 is between 0.1 and 0.5 per cent[13] which means that about 5-20 infants may be recalled for TFTs for every one

case of CH. It is true that the higher the recall rate is associated with the greater sensitivity for detection of CH. However, high recall rate not only increases the expense of follow-up system and blood testing but also creates anxiety and worriness for the parents while waiting for the results.

After 3 years of screening, all newborns with cord serum TSH levels between 30 and 40 mU/L had normal TFTs. In addition, there has been no single case of confirmed CH who had cord serum TSH of <50 mU/L. Hence, with confidence, the cut-off value of cord serum TSH was raised to 40 mU/L which decreased the recall rate to 0.43 per cent.

Regarding the follow-up system, most programs initially were incomplete. Therefore, significant percentage of infants with elevated TSH did not return for TFTs. To completely identify infants with CH, improvement of the follow-up system is essential.

In summary, TSH screening in Ramathibodi Hospital during the past 5 years, over 35 thousand infants were screened for CH. The percentage of specimen collection progressively improved from 84 per cent to 95 per cent. The patients' return after recalls increased from 38 per cent to 100 per cent. The optimal cut-off value for cord serum TSH based on the population in Bangkok and the current hormone assay is 40 mU/L. By using this cut-off value, the recall rate is about 0.43 per cent. This screening program was proven to be cost-beneficial[2]. It is essential to emphasize that the program may not be cost-beneficial if the coverage of screening and the follow-up system are incomplete.

In conclusion, this five-year study demonstrated the incidence of CH in infants born in Ramathibodi Hospital was about 1:3,000 live-births. To prevent a social burden of raising mentally handicapped children, it is time to organize routine thyroid screening program nationwide.

(Received for publication on October 15, 1999)

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การตรวจคัดกรองภาวะพร่องธัยรอยด์ฮอร์โมนแต่กำเนิด: ประสบการณ์ 5 ปี ในโรงพยาบาลรามาธิบดี

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วัตถุประสงค์ เพื่อให้การวินิจฉัยภาวะพร่องธัยรอยด์ฮอร์โมนแต่กำเนิด และให้การรักษาโรคตั้งแต่แรกเกิด โดยที่ทารกยังไม่แสดงอาการ

วิธีการศึกษา เก็บเลือดจากสายสะดือของทารกเพื่อตรวจระดับฮอร์โมนธัยโรโทรปิน (TSH) โดยเริ่มโครงการตั้งแต่เดือนตุลาคม 2536 ถึงธันวาคม 2541 ทารกแรกเกิดจำนวน 35,390 คน ได้รับการตรวจ TSH จากเลือดสายสะดือ ทารกที่มีระดับ TSH มากกว่า 30 mU/L จะถูกติดตามกลับมาตรวจฮอร์โมนธัยร็อกซิน (T_4), ฟรีธัยร็อกซิน (FT_4) และ TSH ทารกที่มีความผิดปกติจะได้รับการตรวจ thyroid scan และ uptake เพื่อหาสาเหตุของโรค

ผลการศึกษา พบผู้ป่วย 12 ราย คิดเป็นอุบัติการ 1:2,949 ของการเกิดมีชีพ ผู้ป่วยทั้งหมดไม่มีอาการตอนแรกเกิด มี 1 รายซึ่งเป็นทารกเกิดก่อนกำหนดได้รับการวินิจฉัยเป็นโรคพร่องธัยรอยด์ฮอร์โมนเมื่ออายุ 2 เดือน เนื่องจากระดับ TSH ในเลือดจากสายสะดือไม่สูง

เมื่อใช้ระดับ TSH ที่มากกว่า 30 mU/L และ 40 mU/L เป็นเกณฑ์ในการเรียกทารกที่สงสัยจะเป็นโรคกลับมาตรวจ พบว่าอัตราการติดตามกลับมาตรวจยืนยันการวินิจฉัยโรคเท่ากับร้อยละ 1.1 และ 0.43 ตามลำดับ ผู้ป่วยทุกรายมีระดับ TSH จากสายสะดือมากกว่า 50 mU/L ยกเว้น 1 รายที่เป็นทารกเกิดก่อนกำหนด ดังนั้นระดับ TSH ที่ใช้เป็นเกณฑ์ในการติดตามทารกกลับมาตรวจ จึงเปลี่ยนเป็น 40 mU/L ตั้งแต่เดือนมกราคม พ.ศ.2540

ปัญหาและอุปสรรคสำคัญที่พบในการดำเนินโครงการนี้คือ การเก็บเลือดไม่ครบทุกคนและการติดตามผู้ป่วยกลับมาตรวจยืนยันการวินิจฉัยโรคไม่ครบถ้วน ดังนั้นในปี พ.ศ.2539 จึงปรับปรุงระบบการติดตามให้สมบูรณ์ขึ้น ทำให้จำนวนการเก็บเลือดและผลการติดตามเพิ่มขึ้นจากร้อยละ 84 และ 38 ในปี พ.ศ.2537 เป็นร้อยละ 96 และ 100 ในปี พ.ศ.2541 ตามลำดับ

สรุป อุบัติการของภาวะพร่องธัยรอยด์ฮอร์โมนแต่กำเนิดในโรงพยาบาลรามาธิบดี พบประมาณ 1:3,000 ระดับ TSH จากเลือดสายสะดือมากกว่า 40 mU/L เป็นเกณฑ์ที่เหมาะสมในการติดตามทารกกลับมาตรวจยืนยันการวินิจฉัยโรค การปรับปรุงระบบการติดตามผู้ป่วยเป็นสิ่งสำคัญที่ทำให้โครงการสมบูรณ์ขึ้น สามารถติดตามผู้ป่วยกลับมาได้มากขึ้นและให้การรักษาได้รวดเร็วขึ้น

คำสำคัญ : ภาวะพร่องธัยรอยด์ฮอร์โมนแต่กำเนิด, การตรวจคัดกรอง, ประสบการณ์ 5 ปี ในโรงพยาบาลรามาธิบดี

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