Thyrotropin Screening for Congenital Hypothyroidism in Queen Sirikit National Institute of Child Health, Thailand (During year 1995-2000)

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Abstract

Objectives : To detect newborns with congenital hypothyroidism (CH) by TSH screening and to treat the affected infants as early as possible. To find the incidence of CH in neonates born at Rajavithi Hospital from 1995 to 2000. The effects of thyroid pathology, ages at the initiation of treatment, associated conditions, and severity of CH on the intellectual outcome of the patients were also analyzed.

Study designs : Thyrotropin (TSH) screening for CH in Queen Sirikit National Institute of Child Health was done in neonates born at Rajavithi Hospital from 1995 to 2000. Infants with elevated TSH level of greater than 25 mU/L were recalled for tests including serum T_4, TSH and roentgenogram of bone age. Infants with CH were treated with levothyroxine 10-12 Ug/Kg/day : growth and development, serum T_4, TSH were followed-up every 3 months for at least 2 years to keep serum T_4 between 10-14 Ug/dL and serum TSH below 6 mU/L. Levothyroxine was discontinued for 4 weeks when the infants were over 2 years old. Serum T_4, TSH, thyroid scan, and uptake were then performed on these infants. The patients must be euthyroid at the time of the intelligence testing. The Stanford Binet or Vineland Social Maturity scale was used to evaluate the patient's intelligence between the ages of 2 and 5 years.

Results : From 1995 to 2000, 62,681 neonates were screened for CH. The incidence of CH was 1 : 4,178 live births. The sex ratio female : male 2 : 1. Fifteen infants with CH were started on levothyroxine 10-12 Ug/Kg/day orally once a day. The age of initiation of treatment was between 2-8 weeks. There were 4 patients with lingual thyroid, 4 patients with thyroid hypoplasia, 2 patients with thyroid aplasia and one patient with organification defect. The average intelligence score was 93.8. The factor that significantly affected the intellectual outcome of the patients was associated with adverse conditions such as prematurity with complications, epilepsy and family disruption ($p<0.05$).

Conclusion : The results indicate that congenital hypothyroidism is common in Thailand. Intellectual outcome in these patients with CH has been improved by neonatal screening and giving an initial high dose of levothyroxine treatment as early as possible.

Key word : Thyrotropin Screening, Congenital Hypothyroidism at Queen Sirikit National Institute of Child Health, Intelligence Quotient, Neonatal Diagnosis, Age

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Congenital hypothyroidism (CH) is one of the most common endocrine diseases of children. The incidence of CH worldwide is approximately 1 : 4,000 live births with a range of 1 : 2,000 to 1 : 7,000 live births[1-4]. Recent reports from Southeast Asian countries showed the incidence of CH varied from 1 : 600 to 6,246 live births[5-10].

The clinical findings of CH in the early months of life are nonspecific e.g. constipation, lethargy, poor feeding and prolonged neonatal jaundice etc. However, delayed diagnosis and treatment of CH will cause irreversible mental deficiency and neurological deficit[11]. Churesigaew S. reported that only 20.4 per cent of children with CH received treatment before 3 months of age[12]. Kleine et al showed the average intelligence quotient (IQ) scores of infants treated before 3 months was 89, 3-6 months 70 and after 7 months the average IQ was only 54. Besides, these infants will have neurological deficit i.e. spasticity, hyperkinesis, short attention span, speech defect, ataxia and irreversible mental retardation from delayed diagnosis and treatment[13]. Therefore, screening for CH in neonates is universally accepted as necessary and has also proved to be cost-benefit[6].

The purpose of this study was to evaluate the incidence of CH and the intellectual outcomes of those patients detected by neonatal screening at Queen Sirikit National Institute of Child Health in Thailand. The relationships between intellectual outcome and pathology of the thyroid, ages at initiation of treatment and severity of hypothyroidism were also analyzed.

SUBJECTS AND METHOD

The TSH screening program was initiated at Queen Sirikit National Institute of Child Health in 1995. Initially screening was done on cord blood of neonates born at Rajavithi Hospital by the laboratory of Rajavithi Hospital. The TSH level was measured by using radioimmunometric assay. From June 1996 TSH screening was done on dried blood by the laboratory of the Department of Medical Sciences, Ministry of Public Health. The blood specimens were taken from the infants at the age of 2-3 days. Radioimmunometric assay was used to measure the TSH level. The cut-off level for patient recall was 25 mU/L. Serum T_4, TSH bone age X-rays were done on patients with an abnormal screening test. If the value of serum T_4, TSH was abnormal, the neonate was placed on levothyroxine 10-12 Ug/Kg/day orally once a day. Serum T_4, TSH were again repeated 2-4 weeks after initiation of treatment. If serum T_4 was between 10-14 Ug/dl and serum TSH was less than 6 mU/L, the same dosage of levothyroxine was continued. Serum T_4, TSH was checked every 3 months during the first 2 years of life, when the infants were 2-3 years old levothyroxine was dis-

continued for 4 weeks. Determination of serum T_4, serum TSH, ^{131}I uptake and technetium-99 m scan of the thyroid gland was then performed on these infants. If the test was normal, levothyroxine was discontinued. The Stanford Binet or Vineland Social Maturity Scale was used to evaluate the intelligence quotient (IQ) or the social quotient (SQ) scores in euthyroid patients between the ages of 2 and 5 years.

Statistical analysis of data related to intellectual outcome was performed using student's *t*-test and one-way analysis of variance (ANOVA) and Fisher Exact. A p-value of less than 0.05 was considered statistically significant.

RESULTS

From May 1995 to December 2000, 80,085 infants were born at Rajavithi Hospital and 62,681 neonates were screened for CH. The average coverage of thyroid screening was 78.27 per cent. The coverage increased significantly from 44.12 per cent in 1995 to greater than 94 per cent in the last 3 years as shown inTable 1. The incidence of CH in this series was 1 : 4,178 live births.

Infants with elevated TSH levels greater than 25 mU/L were recalled for confirmation of CH. The average recall rate was 0.47 per cent. The return rate for repeated test has increased progressively from 47.87 per cent in 1995 to 89.47 per cent in 2000 (Table 2).

Of 62,681 neonates screened for CH, 15 patients with CH were found (Table 3). There were 10 females and 5 males. The sex ratio F : M = 2 : 1. The etiology of CH detected by thyroid scan and uptake showed that 2 patients with athyreosis, 4 patients with lingual thyroid, 4 patients with thyroid hypoplasia and 1 patient with organification defect. Serum T_4 were between <0.23 to 13.79 Ug/dl. Serum TSH values were 6.98 to >100 mU/L. X-rays of bone age showed normal bone age in 9 patients, and delayed bone age in 6 patients. Ages at start of treatment were 2-4 weeks in 11 patients, over 4-8 weeks in 4 patients. Case number 1 had a history of disruptive family. The patient's parents planned to divorce. Case number 7 was a premature baby with many complications. Case number 11 had patent ductus arteriosus, congestive heart failure and epilepsy.

Table 1. Coverage of TSH screening from May 1998 - to December 2000.

Year	Total births	No. Screened	%
1995 (May-December)	12,155	5,363	44.12
1996	15,776	10,684	67.72
1997	14,309	9,875	64.10
1998	13,396	12,725	94.99
1999	12,191	11,981	98.28
2000	12,258	12,053	98.32
68 mo.	80,085	62,681	78.27

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

Year	No. Screened	TSH>25 mU/L	Recall rate (%)	Return rate for repeated test (%)
1995 (May-December)	5,363	94	1.75	47.87
1996	10,684	94	0.88	67.02
1997	9,875	15	0.15	100.00
1998	12,725	26	0.20	80.77
1999	11,981	34	0.28	94.12
2000	12,053	19	0.16	89.47
Total	62,681	293	0.47	-

Table 3. Laboratory findings in 15 patients with CH diagnosed by TSH screening, IQ, SQ and ages at start of treatment.

No.	Screening TSH mU/L	T_4 Ug/dL	TSH mU/L	X-Ray bone age	Thyroid scan up take	Ages of start of treatment	IQ or SQ
1+	43.01	9.97	81.82	Normal	Ectopia	4	80
2	135.6	0.75	>100.0	Delayed	Organifi-cation defeet	3	103
3	34.87	6.0	>50.0	Normal	Athyreosis	4	113
4	97.81	4.18	>100.0	Normal	Ectopia	4	94
5	>191.11	0.9	>100.0	Normal	Athyreosis	4	92
6	191.0	4.4	92.11	Normal	Ectopia	5	92
7+	26.01	13.79	13.19	Delayed	Hypoplasia	8	84
8	47.39	6.44	6.98	Delayed	Hypoplasia	4	104
9	47.4	11.4	32.3	Normal	Hypoplasia	4	91
10	>100.0	<1.0	>100.0	Delayed	Hypoplasia	8	99
11+	191.0	0.602	17.28	Normal	Ectopia	8	80
12	>171.0	<0.23	>100.0	Delayed	-	4	-
13	229.82	5.43	>100.0	Delayed	-	4	-
14	51.08	9.15	>35.1	Normal	-	2	-
15	>100.0	1.5	>100.0	Normal	-	3	-

+ SQ was used because IQ could not be tested

Table 4. IQ or SQ scores in 11 patients with CH in relation to initial serum T_4, X-ray bone age.

IQ or SQ	T_4 Concentration		X-Ray bone age	
	<2 Ug/dL	>2 Ug/dL	Delayed	Normal
>90 +	3	5	2	6
80-89 ++	1	2	1	2
	Fisher Exact p = 0.72		Fisher Exact p = 0.66	

\+ IQ>90 = normal
++ IQ Dull average or dull normal

He received treatment rather late at 8 weeks of age. Case number 12 was lost to follow-up. Case number 13 has Down's syndrome. She was 13 months old at the time of study.

There were only 3 patients with dull normal intelligence excluding 1 patient with Down's syndrome who has not had an IQ test yet. The average intelligence score of this series was 93.8 which is normal.

Table 4 shows IQ or SQ scores in 11 patients with CH in relation to initial serum T_4 <2 Ug/dl or >2 Ug/dl, delayed or normal bone age. There was no significant difference between the patients with IQ >90 and IQ 89-80, normal or delayed X-ray bone age.

Table 5 shows IQ or SQ scores in patients with mild CH (ectopia, thyroid hypoplasia), severe CH (athyreosis, dyshormonogenesis)[14] and also in relation to associated adverse conditions, ages at start of treatment (<4 weeks, 4-8 weeks).

Only patients with adverse conditions had IQs between 80-89 ($p>0.05$).

DISCUSSION

The incidence of CH in this study was 1 : 4,178 live births. The sex ratio female : male was 2 : 1. Ectopic thyroid gland, and thyroid hypoplasia were the most common cause of CH. This finding is similar to other studies[4-10]. In previous studies, pathology and mental outlook varied among patients with various types of CH not detected by neonatal screening i.e. patients with ectopic glands had the best prognosis, and athyreosis was the worst [11,13-15]. Hsiao HP et al's report showed patients

Table 5. IQ or SQ scores in patients with mild CH (ectopia, hypoplasia) severe (athyreosis, dyshormonogenesis) with and without adverse conditions, ages at start of treatment.

IQ or SQ	mild CH	severe CH	Adverse * conditions	No adverse conditions	Age at start of treatment	
					<4 wks	4-8 wks
>90	5	3	0	8	6	2
80-89	3	-	3	0	1	2
	Anova p = 0.12		Anova p = 0.01		Anova p = 0.59	

* $p<0.05$

with initial serum T_4 <2 Ug/dL at the time of diagnosis had lower IQs than those with initial serum T_4 >2 Ug/dL ($p<0.05$). Patients with delayed bone age at birth had lower IQs than those with normal bone age ($p<0.05$)[14]. The findings from the present study did not agree with Hsiao HP et al 's findings [14]. Only the adverse associated conditions of the patients had significantly effect in lowering IQs than the patients without adverse conditions ($p<0.05$). The present study also suggests that early treatment reduced the difference in IQs among the various confounding factors. Bongers JJ et al's data suggested using higher dosage of levothyroxine (above 9.5 Ug/Kg/d) than previously used in the newborns 2 weeks after birth resulted in normal IQs of patients with CH, irrespective of the severity of the disease [15]. The patients in the present study were placed on levothyroxine 10-12 Ug/Kg/d and had regular serum T_4, TSH and followed-up every 3 months until 2-3 years of age. That may be why most of the patients had normal IQs. One patient with athyreosis even had an IQ of 113 which is considered bright normal.

In conclusion, the present study has shown that the intellectual outcome in patients with CH has been improved by neonatal screening and only associated adverse conditions are the most important prognostic factors affecting the intellectual outcome of the patient.

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การตรวจคัดกรองภาวะพร่องฮอร์โมนธัยรอยด์แต่กำเนิดที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี พ.ศ. 2538–2543

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วัตถุประสงค์ : เพื่อให้การวินิจฉัยภาวะพร่องธัยรอยด์ฮอร์โมนแต่กำเนิด และให้การรักษาโรค ตั้งแต่แรกเกิด โดยที่ทารกยังไม่แสดงอาการ ทำให้ทราบอุบัติการณ์ของโรค นอกจากนี้ยังหาสาเหตุปัจจัยที่ทำให้ผู้ป่วยที่ขาดธัยรอยด์ฮอร์โมนแต่กำเนิดมีระดับสติปัญญาต่างกัน

วิธีการศึกษา : เก็บเลือดเพื่อตรวจระดับฮอร์โมนธัยโรโทรปิน (TSH) โดยเริ่มโครงการ ตั้งแต่เดือนพฤษภาคม 2538 ถึง ธันวาคม 2543 ทารกแรกเกิด จำนวน 62,681 คน ได้รับการตรวจ TSH ทารกที่มี TSH มากกว่า 25 mU/L จะถูกติดตามมาตรวจฮอร์โมน์ธัยร็อกซิน (T_4) และ TSH ทารกที่มีความผิดปกติจะได้รับยา Levothyroxine 10–12 Ug/กก/วัน ตรวจ T_4, TSH, การเจริญเติบโตของผู้ป่วยตลอดทั้งพัฒนาการ, ทุก 3 เดือน โดยปรับยาให้ T_4 อยู่ระหว่าง 10–14 Ug/dl และ TSH น้อยกว่า 6 mU/L, เมื่อทารกอายุ 2–3 ปี หยุดยา levothyroxine 4 สัปดาห์ แล้วตรวจ T_4, TSH, thyroid scan และ uptake ตรวจระดับสติปัญญาเด็ก เมื่อผู้ป่วยปกติแล้ว ศึกษาปัจจัยที่อาจมีผลต่อระดับสติปัญญา ของเด็ก คือ อายุที่เริ่มให้การรักษา, ระดับ T_4, เกณฑ์อายุกระดูก, สาเหตุของภาวะพร่องธัยรอยด์ฮอร์โมน, ภาวะแทรกซ้อนต่าง ๆ โดยใช้ ANOVA และ Fisher Exact test.

ผลการศึกษา : พบผู้ป่วย 15 ราย มีภาวะพร่องรอยด์ฮอร์โมนแต่กำเนิด คิดเป็นอุบัติการณ์ 1 : 4,178 ของการเกิดมีชีพ เพศหญิง : เพศชาย 2 : 1 อายุที่เริ่มรักษา 2–8 สัปดาห์ พบต่อมธัยรอยด์อยู่ผิดที่ที่โคนลิ้น 4 ราย, ต่อมธัยรอยด์ฝ่อ 4 ราย, ไม่มีต่อมธัยรอยด์ 2 ราย, ต่อมธัยรอยด์สร้างฮอร์โมนไม่ได้ (organification defect) 1 ราย ระดับสติปัญญาเฉลี่ยของผู้ป่วย 93.8 ปัจจัยที่มีผลต่อระดับสติปัญญาคือภาวะผิดปกติของผู้ป่วย เช่น คลอดก่อนกำหนดและโรคแทรกซ้อน, ลมบ้าหมู ปัญหาขาดความอบอุ่นการเลี้ยงดูในครอบครัว

สรุป : ภาวะพร่องธัยรอยด์ฮอร์โมนแต่กำเนิดที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ระหว่างปี 2538–2543 พบ 1 : 4,178 การตรวจคัดกรองภาวะนี้ในเด็กแรกเกิดและให้การรักษาด้วยยา levothyroxine ขนาด 10–12 ไมโครกรัม/กิโลกรัม/วัน ภายใน 4 สัปดาห์ หรืออย่างช้าไม่เกิน 8 สัปดาห์ จะป้องกันภาวะปัญญาอ่อนในเด็กที่เป็นโรคนี้ได้

คำสำคัญ : ภาวะพร่องธัยรอยด์ฮอร์โมนแต่กำเนิด, การตรวจคัดกรองที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ในเด็กแรกเกิด, ปัจจัยที่มีผลต่อระดับสติปัญญา

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