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The etiologies and incidences of congenital hypothyroidism before and after neonatal TSH screening program implementation: a study in southern Thailand

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Abstract

Background: Congenital hypothyroidism (CH) is one of the common causes of intellectual disability which can be prevented by early detection of an elevated thyroid stimulating hormone (TSH) level in the newborn and by treatment with thyroxine. In Thailand, neonatal TSH screening was implemented nationwide in 2005. The objective of the study was to determine the etiologies and the estimated incidences of CH in southern Thailand before and after the implementation of a neonatal TSH screening program in 2005.

Methods: The medical records of pediatric patients who were diagnosed with primary CH at Songklanagarind Hospital during 1995–2013 were retrospectively reviewed. The study was divided into two time periods: study period 1 (SP1) (1995–2004) and study period 2 (SP2) (2005–2013), the time before and after TSH program implementation.

Results: The most common form of CH during SP1 was overt permanent CH (66%), mostly caused by athyreosis or ectopic thyroid. In SP2, the most common form of CH was mild permanent CH (39%) (mostly due to dys-hormonogenesis), followed by overt CH (32%) and transient CH (29%). The overall annual estimated incidence of CH per 10,000 live births in Songkhla Province was 1.69 (1:5021) in SP1, increasing to 4.77 (1:2238) in SP2; in all 14 provinces in southern Thailand, the estimated incidence was 1.24 (1:8094) in SP1 and 2.33 (1:4274) in SP2.

Conclusions: Neonatal TSH screening has a significant impact on the increased detection of the mild form of permanent and transient CH cases, which may be important

for the prevention of brain damage from less severe CH although this remains to be documented.

Keywords: athyreosis; congenital hypothyroidism; neonatal TSH screening; thyroid dys-hormonogenesis; transient congenital hypothyroidism.

Introduction

Congenital hypothyroidism (CH) is one of the common causes of intellectual disability which can be prevented by early detection of an elevated thyroid stimulating hormone (TSH) level in the newborn period and by treatment with thyroxine supplementation. Following the neonatal TSH screening program established in most countries with high resources during 1990–2000, the reported incidence of CH worldwide has increased from 1:4000 to 1:2000–1:3000 [1, 2].

In Thailand, the incidence of primary CH was first studied as a pilot project in southern Thailand during 1982–1984, and a rate of 1:4000 live births was determined [3]. Following that initial study, there were a number of studies examining CH incidence from various single university hospitals in Thailand during 1990–2002 which found rates from 1:2500 to 1:4000 [4–9]. Neonatal TSH screening in Thailand was then implemented nationwide in 2004–2005 by the Ministry of Public Health [10]. Based on the national guideline for CH issued by the Royal College of Pediatricians of Thailand and the Thai Society of Pediatric Endocrinology [11], neonates who have TSH screening at 48–72 h after birth with a result of ≥ 25 mU/L are recalled for a confirmatory test. If the confirmatory TSH level is ≥ 10 mU/L, CH is diagnosed and thyroxine treatment is begun. At 3 years of age, the thyroxine is discontinued for 4–8 weeks and the thyroid function test (TFT) is re-performed. From the results of TFT, children with TSH ≥ 10 mU/L are diagnosed as having permanent CH and then thyroid scintigraphy is performed, and thyroxine treatment is indicated lifelong.

Songklanagarind Hospital is the major tertiary care center in southern Thailand and is the only hospital in the region where a 99m technetium thyroid scan can be

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performed. Most CH cases in southern Thailand are referred to our institute for a thyroid scan at 3 years of age. Thus, we are in a good position to determine the estimated incidence of CH before and after the TSH screening program implementation and also to determine the changes in the etiologies of CH during the last 20 years in southern Thailand.

Materials and methods

Patient recruitment

The medical records of patients aged 0–15 years who were diagnosed with primary CH (retrieved by International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] code of E03) at Songklanagarind Hospital during 1995–2013 were retrospectively reviewed. Data collection from the medical records included age at diagnosis, initial TSH screening level, confirmatory free thyroxine (FT_4) and TSH levels, date and dosage of initial thyroxine treatment, date of thyroxine discontinuation, date of re-evaluation of FT_4 and TSH, date and results of thyroid scan and the final diagnosis of CH.

We divided the timing of the study into two periods according to the national TSH screening program implementation: study period 1 (SP1) 1995–2004, the time before the neonatal TSH screening program implementation, and study period 2 (SP2) 2005–2013, the time after the TSH screening program was completely implemented in the 14 provinces of southern Thailand.

Neonatal TSH screening program

Since the newborn TSH screening was implemented in 2004–2005, each neonate has had TSH screening by a blood test in a filter paper card at 48–72 h after birth. Based on the national guideline for CH by the Royal College of Pediatricians of Thailand and the Thai Society of Pediatric Endocrinology [11], neonates who show an initial whole blood TSH level ≥ 25 mU/L are recalled for a confirmatory test for serum FT_4 and TSH at 7–14 days. Neonates who show an initial TSH level ≥ 25 mU/L and confirmatory TSH levels < 10 mU/L 2 times 1–2 weeks apart are considered normal and no further action is taken. CH is diagnosed if the confirmatory TSH level is ≥ 10 mU/L, and then treatment with thyroxine 10–15 $\mu\text{g/kg/day}$ is begun with regular follow-up assessment. During the follow-up period, FT_4 and TSH are checked for thyroxine dosage adjustment every 2–3 months in the first year and every 3–6 months in the second and third years. At 3 years of age, serum FT_4 and TSH are re-evaluated after discontinuation of thyroxine for 4–8 weeks and the patient is classified into one of the three categories based on the TSH level as follows:

1. Transient CH if the TSH is < 5 mU/L at every 6-month interval for a further 2 years, then the patient is discharged from the treatment.
2. Permanent CH if the TSH is ≥ 10 mU/L, with a further subclassification of mild or overt CH for TSH levels between 10 and 40 mU/L or > 40 mU/L, respectively [12]. Thyroid scintigraphy is also performed to determine the etiology of CH as eutopic, ectopic or thyroid dysplasia. Patients diagnosed with permanent CH are started on lifelong thyroxine therapy.

3. Subclinical CH if the TSH is 5–10 mU/L, and the patient will be followed-up for FT_4 and TSH every 6 months for a further 2 years. If the TSH rises to ≥ 10 mU/L, or persists at 6–10 mU/L, then the patient is diagnosed as having mild permanent CH and is scheduled for thyroid scintigraphy and will be treated with lifelong thyroxine therapy. Patients who have a TSH level < 5 mU/L during the 2-year follow-up are classified as transient CH and discharged from the treatment.

In our institute, thyroid screening in preterm neonates was implemented in 2010. The TSH level is measured twice in preterm neonates: first at 72–96 h after birth and second at 2–3 weeks of age. If the second TSH level is ≥ 10 mU/L, the infant will have FT_4 and TSH performed again in a further 2 weeks. If the TSH remains persistently high at ≥ 10 mU/L, the infant will be started on thyroxine 10–15 $\mu\text{g/kg/day}$. FT_4 and TSH will be followed-up for thyroxine dosage adjustment every 2–3 months in the first year and every 4–6 months in the second and third years, and at 3 years of age, the thyroxine is discontinued for 4–8 weeks and FT_4 and TSH are re-performed, and the diagnosis of CH is then evaluated as in the term neonates described above.

Measurement of neonatal screening TSH levels

The blood samples for the neonatal TSH screening measurements in this study were sent in filter papers to the Regional Medical Sciences Center (Songkhla), Department of Science, Ministry of Public Health. The TSH assays were performed using an immunoradiometric assay (IRMA) which has a sensitivity of 0.2 mU/L, an intra-assay coefficient of variation of 4–6% and an inter-assay coefficient of variation of 7–9% [13].

Confirmatory thyroid function tests

During 1994–2006, FT_4 was measured by radioimmunoassay (RIA) and TSH by IRMA. The minimal detectable levels of FT_4 and TSH were 0.02 ng/dL and 0.005 mU/L, respectively. The inter-assay and intra-assay coefficients of variations of FT_4 were 6.6% and 2.9%, respectively, and those of TSH were 5.4% and 2.1%, respectively. After 2007, FT_4 and TSH were measured by electrochemiluminescence immunoassay (ECLIA) using a Modular Analytics E170 machine (Roche Diagnostics, Mannheim, Germany) with an intra-assay coefficient of variation of 1.6–5.0%, and an inter-assay coefficient of variation of 1.7–5.8%.

Statistical analysis

The data were analyzed and presented as number and percentage or median with interquartile ranges (IQRs). The estimated annual incidences of CH were calculated and expressed as the number of cases per 10,000 live births in Songkhla Province alone and in all 14 provinces in southern Thailand together. The analysis of variance (ANOVA) or chi-square (χ^2) test was used to compare differences in categorical data among the groups in each time period. The student t-test, Mann-Whitney U-test or Kruskal-Wallis test was used for analysis of continuous data with normal distribution or nonparametric distribution. The statistical findings were considered to be significant when the p-value was < 0.05 .

Ethical approval

The protocol of this study was approved by the Institutional Review Board and the Ethics Committee of the Faculty of Medicine, Prince of Songkla University. A written informed consent was obtained from the children's parents for permission to use the clinical data for this study.

Results

There were 491 CH patients recruited. Of these, 38 were excluded: 34 with the confirmatory TSH level <10 mU/L and four cases of secondary CH (detected by clinical features of micropenis and/or hypoglycemia). Congenital primary CH was diagnosed in 453 cases: 165 cases (36.4%) in SP1 and 288 cases (63.6%) in SP2. Of the total, 119 patients (26.3%) were from Songkhla Province where our institute is located.

Incidence of CH

During 1995–2013, there were 2,566,489 live births in the 14 provinces of southern Thailand: 1,335,536 during the SP1 period and 1,230,953 during the SP2 period. Of these, 391,575 live births (15.3%) were in Songkhla Province. For the incidence of CH, we used the term 'estimated annual incidence' due to the possibility of incomplete referral of CH cases from the other provinces besides Songkhla which might result in a lower-than-expected actual incidence of CH in southern Thailand. Because of this concern, we decided to determine the overall estimated annual incidence in all provinces together in southern Thailand (including Songkhla), but only single provincial incidence in Songkhla Province where our institute is located, as we were confident of the tracking system in this province confirming that $>95\%$ of the cases from Songkhla had a thyroid scan done in our institute.

The overall annual estimated incidence of CH per 10,000 live births in southern Thailand was 1.24 in SP1 (1:8094) and 2.33 (1:4274) in SP2. In Songkhla Province, the overall annual estimated incidence per 10,000 live births of CH was 1.69 (1:5021) in SP1 and 4.77 (1:2238) in SP2. The estimated incidence of CH in Songkhla during 1995–1999 was the same as in the overall 14 provinces in southern Thailand, increasing 1.5-fold during 2000–2009 and further increasing 2.5–3-fold during 2010–2013. It is notable that the increases in the annual estimated incidence of CH in Songkhla Province and all 14 provinces were due to the increases in the number of CH children

with a history of being preterm while the number of term CH children was about the same as during 2003–2011 (Figure 1A and B).

Changes in etiologies of CH

Of the total 453 patients, 91 cases (20.1%) were classified as transient CH, 160 (35.3%) as mild permanent CH and 202 (44.6%) as severe permanent CH (Table 1). Thyroid scans were performed in 334 patients with permanent CH (92.3%), which revealed eutopic thyroid in 137 cases (41.0%) of which 34 cases (24.8%) were found to have an increased thyroid size, ectopic thyroid in 109 cases (32.6%), athyreosis in 77 cases (23.1%) and thyroid hypoplasia in 11 cases (3.3%). The final diagnoses of CH patients in the 14 provinces in southern Thailand (Figure 2A) and in Songkhla (Figure 2B) showed similar patterns in each category of CH in both SP1 and SP2 periods. The most

Figure 1: Estimated incidence of congenital hypothyroidism (CH) in Thailand.

(A) The estimated incidence of CH per 10,000 live births in the 14 provinces in southern Thailand during 1995–2013. (B) The estimated incidence of CH per 10,000 live births in Songkhla during 1995–2013.

Table 1: Comparison of congenital hypothyroidism rates between patients during 1995–2004 and 2005–2013.

Characteristics	1995–2004 (n=165)	2005–2013 (n=288)	p-Value
Male, n (%)	72 (43.6)	137 (47.6)	0.36
No. of neonates with TSH screening, n (%)	43 (26.1)	288 (100)	<0.001
No. of preterm neonates, n (%)	1 (0.6)	44 (15.3)	<0.001
Screening TSH level, IU/L	100 (26.5, 100)	59.5 (33, 100)	<0.001
Age at confirmation, days	67.5 (28, 109)	22 (16, 32)	<0.001
Confirmatory TSH level, IU/L	100 (26, 100)	20.3 (33, 100)	<0.001
Age at thyroxine treatment, days	57 (26, 769)	24 (18, 34)	<0.001
Final diagnosis, n (%)	n = 165	n = 288	
– Transient hypothyroidism	8 (4.8)	83 (28.8)	<0.01
– Mild permanent hypothyroidism	48 (29.1)	112 (38.9)	
– Overt permanent hypothyroidism	109 (66.1)	93 (32.3)	
No. of patients with thyroid scan, n (%)	n = 152	n = 182	
– Athyreosis	51 (33.6)	26 (14.3)	<0.01
– Hypoplasia	9 (5.9)	2 (1.1)	
– Ectopic thyroid	51 (33.6)	58 (31.9)	
– Dyshormonogenesis	41 (26.9)	96 (52.7)	

Data are shown as median (IQR) or number (percentage) where appropriate. TSH, thyroid stimulating hormone.

Figure 2: Estimated incidence of each type of congenital hypothyroidism (CH) in Thailand.

(A) Estimated incidence per 10,000 live births of each type of CH in the 14 provinces in southern Thailand during 1995–2013.

(B) Estimated incidence per 10,000 live births of each type of CH in Songkhla during 1995–2013.

common etiology during SP1 was overt permanent CH (60–70%), followed by mild permanent CH (30–35%) and transient CH (5%). In SP2, the incidence of mild permanent CH and transient CH gradually increased with the proportions of mild permanent CH and transient CH being 30–40% in all CH patients.

The clinical characteristics of the neonates and etiologies of CH were compared between SP1 and SP2. During SP1, 122 patients (73.9%) were diagnosed with CH at the median age of 1.8 years (IQR 0.9, 3.5) and only 43 CH patients (26.1%) had TSH screening during 2001–2004, the time during which TSH screening was a pilot project in southern Thailand. The age at TSH screening, the levels of screened TSH and confirmatory TSH in SP1 were significantly greater than in SP2 (Table 1). Transient CH was significantly more commonly diagnosed in SP2 than in SP1 and about 40% of patients with transient CH during SP2 had a history of preterm birth. Based on thyroid scan results, ectopic thyroid or thyroid dyshormonogenesis was significantly more common etiologies of mild permanent CH in SP2 than in SP1. The increased thyroid size by thyroid scan was found in 15 of 41 patients (36.6%) and 19 of 96 patients (19.8%) with thyroid dyshormonogenesis during SP1 and SP2, respectively. The lower percentage of increased thyroid size in patients with thyroid dyshormonogenesis in SP2 than in SP1 was explained by the early thyroxine treatment in the detected patients.

The clinical characteristics of the patients with transient CH were compared to those with mild permanent CH

Table 2: Comparison of characteristics of patients with transient CH, permanent mild CH and permanent overt CH.

	Transient CH (n=91)	Mild CH (n=160)	Overt CH (n=202)	p-Value
Male, n (%)	49 (53.8)	96 (60.0)	64 (31.7)	<0.01
Birth weight, g	2410 (1420, 3100)	2885 (2448, 3197)	3200 (2900, 3400)	<0.001
Preterm, n (%)	35 (38.5)	9 (5.6)	1 (0.5)	<0.001
Screened TSH level, IU/L	33.5 (27.6, 54.7)	35.5 (29.7, 54.5)	100 (100, 153.2)	<0.001
Confirmed FT ₄ level, ng/dL	1.28 (1.17, 1.39)	1.27 (1.04, 1.48)	0.28 (0.17, 1.03)	<0.001
Confirmed TSH level, IU/L	16.4 (11.6, 21.5)	17.3 (13.2, 28.3)	100 (75.0, 100)	<0.001
Initial dosage of thyroxine, µg/day	25 (25, 25)	35 (25, 50)	50 (50, 50)	<0.01
Duration of thyroxine treatment, months	28 (18, 34)	36 (20, 47)	39 (24, 50)	0.30
After 4–8 weeks of discontinuation of thyroxine				
– FT ₄ level, ng/dL	1.36 (1.05, 1.54)	1.27 (1.11, 1.45)	0.50 (0.23, 0.99)	<0.01
– TSH level, mU/L	4.23 (3.18, 6.03)	16.82 (9.66, 21.00)	100 (56.63, 100)	<0.001
Thyroid scan, n (%)	–	n=142	n=192	
– Athyreosis		0	77 (40.1)	<0.001
– Hypoplasia		8 (5.6)	3 (1.6)	
– Ectopic thyroid		36 (25.4)	73 (38.0)	
– Dyshormonogenesis		98 (69.0)	39 (20.3)	

Data are shown as median (IQR) or number (percentage) where appropriate. FT₄, free thyroxine; TSH, thyroid stimulating hormone.

and overt permanent CH (Table 2). Transient CH patients had a significantly higher incidence of being preterm births, which also then resulted in significantly average lower gestational age and lower birth weight than patients with mild or severe permanent CH. Patients with overt permanent CH were significantly more likely to be female than male, had significantly greater TSH levels at both the screening and confirmatory tests, had lower FT₄ levels and were treated with higher dosages of initial thyroxine therapy than the patients with mild permanent or transient CH. In the neonatal period, the clinical findings of initial TSH screening, confirmatory TSH and FT₄ levels in patients with transient CH were similar to those with mild permanent CH. At 3 years of age after 4–8 weeks of discontinuation of thyroxine, TSH levels were significantly higher while FT₄ levels were significantly lower in patients with overt permanent CH. Of the total 45 preterm infants with screened TSH ≥ 10 IU/L at the neonatal period, 10 cases (22.2%) were found to have permanent CH at 3 years of age. Of these, six patients had TSH levels < 10 mU/L at 4–8 weeks of discontinuation of thyroxine but the TSH levels gradually increased to ≥ 10 mU/L after 12–18 months of follow-up.

The impact of neonatal TSH screening

During SP2, there was a 2.5–3-fold increase in the detection of mild permanent and transient CH in southern Thailand. It is notable that the annual estimated incidence of overt permanent CH per 10,000 live births was at a constant rate of 1.0–1.5 both in SP1 and SP2 while that of mild permanent CH had a significant 3-fold increase from 0.5–0.8 in SP1 to 1.5–2.0 in SP2. The annual incidence of transient CH significantly increased during 2010–2013 due to the expanded screening program for the preterm infants.

Discussion

The impact of neonatal TSH screening on increased rates of early detection and treatment of patients with permanent CH has been studied in many countries [12, 14, 15]. In Thailand, to our knowledge, our study is the first comparing the CH incidences between pre- and post-neonatal TSH screening implementation. Our study found a 2–3-fold increase in CH detection in southern Thailand and

3–4-fold increase in Songkhla Province after the TSH screening program implementation, and also a significantly earlier age for CH diagnosis and an earlier age for thyroxine treatment. The incidence of overt permanent CH, the most severe form of CH, was stable during the 20-year period of the study, with the most common etiology being thyroid gland maldevelopment (athyreosis and ectopic thyroid). The 2–3-fold increase in the CH incidence during SP2 was due to the detection of mild permanent CH, mostly caused by the disorder of thyroid hormone biosynthesis or dyshormonogenesis. The comparison of the incidences and etiologies of persistent CH from various studies in Thailand are shown in Table 3 [3–10].

The combined incidence of overt and mild permanent CH in our study was 2.5–3.5 per 10,000 (1:2800–4000). The expansion of screening to preterm infants resulted in a 3–4-fold increase in CH incidence to 3–5 per 10,000 live births (1:2000–3000) and about half of the increased incidence was due to the higher detection of transient CH. The significant increase in the incidence of transient and permanent CH in 2012–2013 was due to the increase in referred cases of preterm and term infants with CH for thyroid scintigraphy in our hospital. The patients with overt permanent CH had TSH screening and confirmatory TSH levels >100 mU/L with low FT₄ levels of <0.5 ng/dL. Patients with mild permanent and transient CH had similar screening and confirmatory TSH levels and also confirmatory FT₄ levels that cannot be differentiated between these two conditions in the newborn period. At the age of 3 years, these two conditions can be differentiated after discontinuation of thyroxine for 4–8 weeks as patients with mild permanent CH have elevated TSH ≥10 mU/L while transient CH patients have TSH <5 mU/L.

In Thailand, the cutoff TSH level at the screening time of 48–72 h after birth is 25 mU/L which is higher than the cutoff level in Western countries of 6–10 mU/L at the screening time of 3–4 days [12, 14, 15]. The study of TFT by Mahachoklertwattana et al. [16] showed that the average TSH level in healthy Thai newborns at age 3–4 days was 5.60 mU/L (range 1.1–20.5). The cutoff TSH level of 25 mU/L at 48–72 h after birth is considered to be suitable in Thailand [3–10]. Another study in Thai newborns showed that the average timing for TSH screening was 60 h after birth [13], when TSH was still elevated >10 mU/L. Various studies have found that lowering the cutoff TSH screening level to 10 mU/L can result in an increase in the number of false-positive normal newborns as well as an increase in the detection rate of transient and mild permanent CH [12, 14, 15, 17–19]. A study by Jones et al. [20] in 26 newborns with screened TSH levels of 8.00–9.99 mU/L at 5–6 days after birth found

Table 3: Comparison of the incidence and etiology of congenital hypothyroidism (CH) from various studies in Thailand.

Study year of study, area of study	Newborns receiving TSH screening	Newborns with CH	Incidence	Etiology of CH by thyroid scintigraphy			
				Athyreosis	Hypoplasia	Ectopic	Dyshormonogenesis
Sukthomya et al. [3] 1982–1985, southern Thailand	7814	2	1:4000	1 (50)	–	1 (50)	–
Mahachoklertwattana et al. [4] 1993–1998, Bangkok	35,390	12	1:2949	–	–	–	–
Wasant et al. [5] 1994–1995, Bangkok	18,739	3	1:6246	–	–	–	–
Thaithumyanon et al. [6] 1991–1998, Bangkok	37,262	15 (thyroid scan 14)	1:2484	3 (21.4)	–	8 (57.2)	3 (21.4)
Ratrisawadi et al. [7] 1995–1998, Bangkok	32,407	7	1:4629	–	–	–	–
Churesigaew et al. [8] 1995–2000, Bangkok	62,681	15 (thyroid scan 11)	1:4178	2 (18.1)	4 (36.4)	4 (36.4)	1 (9.1)
Panamonta et al. [9] 2000–2002, Khon Kaen	9558	3	1:3186	1 (33.3)	1 (33.3)	–	1 (33.3)
Charoensiriwatana et al. [10] 1999–2000, Thailand	1,425,025	430	1:3314	–	–	–	–
Our study in southern Thailand 1995–2004, before TSH screening	1,335,536	165 (thyroid scan 152)	1:8094	51 (33.6)	9 (5.9)	51 (33.6)	41 (26.9)
2005–2013, after TSH screening	1,230,953	288 (thyroid scan 182)	1:4274	26 (14.3)	2 (1.1)	58 (31.9)	96 (52.7)

TSH, thyroid stimulating hormone.

that 31% of the cases had mild permanent CH and 65% had transient CH. Hence, lowering the cutoff TSH level to 10–15 mU/L at a screening time of 48–72 h would result in increased false-positive cases and increased recall rate, but would have the benefit of detecting a higher number of cases with a mild form of CH.

In our study, it was difficult to differentiate mild permanent CH from transient CH by the TSH screening level alone and by even following the confirmatory test in both term and preterm infants. In mild permanent CH cases, the disease may not have clinical signs or symptoms during the infancy and early childhood periods, and so early treatment with thyroxine is recommended to ensure the full potential of brain maturation [12, 14, 15, 17–19]. There are no disadvantages of thyroxine treatment on mental development in neonates without hypothyroidism if TFTs are regularly done to ensure that the thyroid hormones remain within the normal ranges. In our study, we found that most cases of transient CH were preterm infants, a finding that was similar to that observed in other studies in other countries [21–24]. However, permanent CH was found in 22.2% of preterm infants with TSH level at 2 weeks of age ≥ 10 mU/L. A study by Srinivasan et al. [22] showed that the incidence of CH in preterm infants was similar to that in term infants. The mildly elevated TSH in preterm infants during the first 2 weeks of life might be a physiological rising and thyroxine treatment during the first 2–3 years of life in patients with transient CH is still questionable in terms of the benefits for mental development. However, delayed TSH elevations in preterm infants with permanent CH have also been reported [25, 26]. Other longitudinal studies in children who were diagnosed with transient CH have reported that these children were at greater risk to have subclinical hypothyroidism in the childhood period [27–29]. Also, genetic mutations of *TPO*, *DUOX2*, *DUOXA2* and *SLC26A4* causing a mild form of dyshormonogenesis have been reported to be a common cause of mild permanent CH [30, 31]. Another possibility for the etiology of transient CH in our study was maternal iodine deficiency during pregnancy, which has also been suggested in a study by Bekhit and Yousef [32]. Our 2007 study in 272 pregnant women in three districts of Songkhla showed that the participating women and their fetuses were at risk of mild iodine deficiency as the median urinary iodine excretion of the pregnant women was 50–100 $\mu\text{g/L}$ and 8.9% of the neonates had TSH levels >5 mU/L [13]. The progress report on iodine deficiency prevention and iodine status in Thailand 2011–2013 from the Department of Health, Ministry of Public Health in Thailand found that each region in Thailand, including southern Thailand, had about 50% mild iodine

deficiency [33]. Hence, to ensure full potential in brain and neurological development during the first 2–3 years of life in newborns suspected of having CH, the practice in our institution is to treat both term and preterm infants who have a TSH level ≥ 10 mU/L at 2–3 weeks of age.

Mild permanent CH can be distinguished from transient CH at the age of 3 years after 4–8 weeks of thyroxine discontinuation [34–36]. Recent studies in Korea have shown that cases with a mild elevation of neonatal TSH level treated with a lower dosage of thyroxine could be re-evaluated earlier at 12–24 months [37, 38]. Following the current guideline by the Royal College of Pediatricians of Thailand [11], thyroxine is discontinued in our patients at 3 years of age and a TFT is performed every 6 months for at least 2 years. Following this protocol during SP2, mild permanent CH was detected in six patients after a follow-up time of 12–18 months, a result consistent with that in other longitudinal studies which found that some patients who were diagnosed with subclinical hypothyroidism during the childhood period had transient CH [27–29].

The current study has some notable strengths and limitations. The main strength was that our study had a large number of CH patients who were longitudinally followed-up for at least 2 years after discontinuation of thyroxine. With this long duration of follow-up, we were able to identify six cases with mild permanent CH who had been initially classified as transient CH. Moreover, the majority of cases in Songkhla with permanent CH (92.3%) had a thyroid scintigraphy performed to enable us to specify the etiology. The limitations are, first, that although during the study period our hospital was the only hospital in southern Thailand where thyroid scintigraphy could be performed, some CH cases still might not have been referred, resulting in a lower than actual incidence of CH in southern Thailand. However, we believe our reported incidence of CH in Songkhla Province to be very accurate, as we have very comprehensive records for this province, and more than 95% of CH or suspected CH cases were referred to our tertiary care center for thyroid scintigraphy. Second, genetic molecular studies of *TPO*, *DUOX2*, *DUOXA2* and *SLC26A4* mutations to identify the specific etiologies of thyroid dyshormonogenesis were not available at the time of the study.

In summary, we conclude that neonatal TSH screening has a significant impact on the increased detection of the mild form of permanent CH and transient CH cases, which may be important for the prevention of brain damage from less severe CH although this remains to be documented.

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