Primary Congenital Hypothyroidism: Clinical Characteristics and Etiological Study

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Forty-eight children with primary congenital hypothyroidism, who attended Chiang Mai University Hospital, during 1977-2000, were reviewed. The female to male ratio was 2:1. The age at diagnosis ranged from 1 month to 12 years 4 months, with 27% of the cases diagnosed within the first three months of life, 37.5% within the first year, and 62.5% after one year of age. Constipation, delayed development and growth, feeding problems, prolonged neonatal jaundice and goiter were more common. Prolonged neonatal jaundice was found in every case diagnosed within the first three months. The other common signs were dry or mottled skin, abdominal distension, macroglossia, short stature, puffy face and umbilical hernia.

Kocher-Debr -Semelaigne syndrome comprised 18.7% of cases with a 2:1 female to male ratio, and it was found in various forms of hypothyroidism. Thyroid scintigrams were done in 47 patients. Thyroid dysgenesis was the most common etiology (80.9%), which consisted of 40.4% athyreosis, 4.3% hypoplasia, and 36.2% thyroid ectopy. Thyroid dyshormonogenesis accounted for 18.9%, in which only 4 of 9 presented with goiter. Two-thirds of these patients showed a positive result to the perchlorate discharge test, indicating an organification defect. All patients had elevated serum TSH level greater than 50 mU/L. The serum T_4 level below 2 μg/dL was observed in 17 of 19 patients with athyreosis, 11 of 17 with thyroid ectopy, and 6 of 9 with thyroid dyshormonogenesis. These findings including retarded bone age were unable to differentiate among different groups of hypothyroidism.

Keywords : *Primary congenital hypothyroidism, Kocher-Debr -Semelaigne syndrome, Thyroid dysgenesis, Athyreosis, Thyroid ectopy, Thyroid dyshormonogenesis,*

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Congenital hypothyroidism (CH) is one of the most common and treatable causes of mental retardation in children. Its incidence, detected by neonatal screening, is rather constant worldwide. The incidence which was reported to be 1:3,000 to 1:4,000 newborns, with the exception of the African-American population in the USA (an incidence of 1: 10,000)[1]. Neonatal thyroid screening has been highly successful in early diagnosis and the improvement of mental prognosis in the hypothyroid neonate. However, some infants with CH have escaped detection from the newborn screening system[2]. This may be related to a screening system error[3], or biological variants[4]. Also, the screening program is not implemented in all countries of the world, but is underway in some countries of Central and South America, Asia, Eastern Europe and Africa. Thus, it is essential that all pediatricians be vigilant in recognizing the early clinical manifestations of congenital hypothyroidism. The purpose of this study was to emphasize the clinical characteristics and define the etiology of CH.

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Patients and Method

Forty-eight infants and children with CH, who attended the Department of Pediatrics, Chiang Mai University Hospital, Thailand during 1977-2000, were studied. Children with hypothyroidism, detected by neonatal screening, and Down syndrome were not included in this study. Recording data included age at diagnosis, clinical manifestations, laboratory

investigations and etiologies. Diagnosis was based on clinical findings and confirmed by elevated thyrotropin and low thyroxine, or free thyroxine levels with retarded bone age. The clinical manifestations presented at the age of diagnosis are shown in Table 1. The clinical data of nine patients with CH and apparent muscular hypertrophy, known as Kocher-Debr -Semelaigne (KDS) syndrome, are shown in Table 2. These included sex, the age at diagnosis, the height age, the bone age, etiologies of CH, and an estimation of the duration of hypothyroidism by subtracting the bone age from the chronological age.

In patients older than 2 years, thyroid scintigraphy was performed before initiation of thyroid hormone supplementation. For those under 2 years of age, therapy was started immediately if thyroid scintigraphy was not available within 24-48 hours. It was performed 4-8 weeks after the discontinuation of thyroxine, when the patients had been treated for at least 24 months. Due to the long duration of the study, two scintigraphic modalities were performed, by using ^{131}I before 1987 and ^{99m}Tc after that time. Thyroid scintigraphies were done in 47 patients. The thyroid scintigraphy result compared to the age of diagnosis is shown in Table 3. There were nine children with a normal location of the thyroid, of either normal or increased size, who underwent the perchlorate discharge test to delineate specific inborn errors. A discharge of greater than 10 percent indicated an organification defect[5].

Table 1. Prevalence of symptoms and signs according to the age of diagnosis

Symptoms and signs	Age at diagnosis (months)					
	0-3	4-6	7-12	13-24	> 24	Total (%)
Total number of cases (%)	13 (27)	3 (6.3)	2 (4.2)	8 (16.7)	22 (45.8)	48 (100)
Jaundice	13	1	1	1	1	17 (35.4)
Constipation	11	2	3	8	19	43 (89.6)
Delayed development	5	2	2	8	18	35 (72.9)
Failure to thrive	1	3	2	7	22	35 (72.9)
Feeding problems	6	1	1	3	9	20 (41.6)
Goiter	1	-	-	-	3	4 (8.3)
Short stature	1	3	2	7	22	35 (72.9)
Infantile proportion	2	2	2	3	19	28 (58.3)
Patent fontanel	7	1	2	7	10	27 (56.3)
Umbilical hernia	11	2	2	6	7	28 (58.3)
Macroglossia	11	3	2	6	15	37 (77.1)
Abdominal distension	11	2	2	6	16	37 (77.1)
Dry or mottled skin	12	2	2	7	16	39 (81.3)
Hypertrophy of muscles	-	-	1	3	5	9 (18.6)
Puffy face	8	1	2	6	13	30 (62.5)

Table 2. Clinical data of 9 patients with Kocher-Debr -Semelaigne Syndrome

Number	Sex	Age at diagnosis(yr)	Height Age(yr)	Bone Age (yr)	Estimated duration of diseases (yr)	Etiology
1	F	1 9/12	11/12	3/12	1 6/12	Hypoplasia
2	M	5 10/12	1 7/12	9/12	5 1/12	Ectopic (SL)
3	F	4 10/12	1 3/12	3/12	4 7/12	Athyreosis
4	M	9 3/12	2 8/12	3/12	9	Ectopic (L)
5	F	1 1/12	5/12	1/12	1	Athyreosis
6	F	7/12	4/12	Newborn	7/12	Dyshormonogenesis
7	F	4 11/12	1 1/12	3/12	4 8/12	Athreosis
8	M	2	7/12	Newborn	2	Dyshormonogenesis
9	F	7 5/12	2 9/12	6/12	6 11/12	Ectopic (SL)

L: Lingual thyroid, SL: Sublingual thyroid

Table 3. The result of the thyroid scintigraphy in 47 patients with CH at the age of diagnosis

Age at diagnosis (months)	Result of thyroid scan				
	Negative	Small	Ectopic	Normal sized	Enlarged sized
0-3	6	-	3	2	2
4-6	3	-	-	-	-
7-12	-	-	-	1	-
13-24	3	1	3	1	-
> 24	7	1	11	-	3
Total (%)	19 (40.4)	2 (4.3)	17 (36.2)	4(8.5)	5 (10.4)

Table 4. Summary of the clinical and laboratory findings in patients with thyroid dyshormonogenesis

Number	Sex	CA (yr)	HA (yr)	Presence of goiter	BA (yr)	T4 (µg/dL)	TSH (mU/L)	Perchlorate discharge (%)
1	M	8	4 7/12	Yes	2	1	ND	< 10
2	F	7/12	3.5/12	No	NB	< 1	> 60	60
3	M	2	6/12	No	NB	< 2	> 50	60
4	F	5 10/12	3 8/12	Yes	2	2.4	> 50	> 60
5	F	8 8/12	6	Yes	5 9/12	2.9	> 60	11.79
6	F	2/12	2/12	No	< 36 FW	8.3*	> 60*	< 10
7	M	2/12	1.2/12	No	< 36 FW	< 0.7	> 60	89.8
8	F	2/12	2/12	Yes	< 36 FW	< 0.7	> 55	< 10
9	M	3/12	1.2/12	No	< 36 FW	0.7	> 60	75

ND; Not done, * the result obtained after medication, < 36 FW: Less than 36 fetal weeks (Absence of distal femoral epiphyses), NB: Newborn (Presence of distal femoral epiphyses)

The clinical and laboratory data of patients diagnosed with thyroid dyshormonogenesis are shown in Table 4.

The laboratory findings of CH patients, with athyreosis, ectopic thyroid or thyroid dyshormonogenesis are compared in Table 5. The Chi-square test was used to compare the frequency of low T_4 levels to each group and it was a statistically significant difference if the P-value was below 0.01.

Results

The patients comprised 32 females and 16 males (ratio 2:1). The age at diagnosis ranged from 1 month to 12 years 4 months old, and was divided into 5 groups as follows: 0-3 months, 4-6 months, 7-12 months, 13-24 months, and > 24 months.

Of the 48 patients, thirteen children (27%) were diagnosed in the first three months of life and 18 (37.5%) within one-year of life. Thirty children (62.5%) were diagnosed after the age of 1- year (Table 1).

In all age groups, the presenting symptoms were constipation, delayed development, failure to thrive, feeding problems, prolonged neonatal jaundice, and goiter, accounting for 89.6, 72.9, 72.9, 41.6, 35.4 and 8.3 percent, respectively. When considering the CH diagnosed in the first three months, prolonged neonatal jaundice, constipation and feeding problems were the more common symptoms, which accounted for 100, 85 and 46%, respectively.

The other common signs, were dry or mottled skin, abdominal distension, macroglossia, short stature, puffy face and umbilical hernia. However, mottling of the skin, macroglossia, abdominal distension with umbilical hernia and patent posterior

Table 5. Comparison of laboratory findings among three groups of CH

Laboratory findings	Number positive/number tested (%)		
	Athyreosis	Ectopic thyroid	Dyshormo-nogenesis
T4 < 2 mg/dL	17/19 (89.5) [A]	11/17 (64.7) [B]	6/9 (66.7)[C]
TSH > 50 mU/L	13/13 (100)	11/11 (100)	8/8 (100)
Delayed bone age	18/19 (94.7)	16/17 (94.1)	9/9 (100)

A vs B, P = 0.186 A vs C, P = 0.34 B vs C, P = 0.74

fontanel were more common in the CH diagnosed within the first three months. The typical face of hypothyroidism was present in 62.5%.

KDS syndrome comprised 18.6% in CH, and a summary of their clinical data is shown in Table 2. There were 6 girls and 3 boys with a female to male ratio of 2:1. The age at diagnosis of KDS children ranged from 7 months to 9 years 3 months. The estimated duration of diseases ranged from 7 months to 6 years 11 months. This syndrome was found in various forms of hypothyroidism, athyreosis, and ectopic thyroid as well as hypothyroidism due to a defect in the thyroid hormone synthesis.

According to the results of thyroid scitigraphy in Table 3, thyroid dysgenesis of athyreosis, thyroid hypoplasia or ectopic thyroid were found in 19, 2 and 17 patients (40.4, 4.3 and 36.2%), respectively, and accounted for the most common (80.9%) etiology. In the ectopic group, 11 patients were observed to have a lingual thyroid, which was not clinically visible in any of them.

There were nine patients (18.9%) with a normal location of the thyroid, of either normal or increased size, and surprisingly, a goiter was found in only four of them. All four patients had negative thyroid antibodies, and one who was diagnosed within 3 months after birth, had a huge thyroid enlargement. Positive results from the perchlorate discharge test, which indicated an organification defect, were found in six patients, and two of three with negative results presented with goiter at the time of diagnosis.

Elevated serum TSH level of greater than 50 mU/L was found in all patients who were tested. The serum T_4 level below 2 μg/dL was observed in 17 of 19 patients with athyreosis, 11 of 17 with ectopic thyroid, and 6 of 9 with thyroid dyshormonogenesis, but the difference was not statistically significant ($P > 0.0$ 1). There was one patient with normal bone age from each of the athyreosis and ectopic thyroid groups.

Discussion

The female preponderance, of 2:1 female to male ratio, is the same as reported elsewhere. The sex predilection of KDS syndrome in the present study is also the same as CH without KDS, but it is different to the study of Najjar SS[6], which showed a male preponderance.

Prolonged neonatal jaundice was the most common symptom in CH diagnosed within 3 months. Neonatal jaundice may present with prolonged or early severe hyperbilirubinemia[7]. In countries where neonatal screening for CH is not yet routine, serum thyrotropin, and thyroxin or free thyroxin should be measured in any infant who exhibits prolonged jaundice or early severe hyperbilirubinemia.

The percentage of KDS patients in this study, which was 18.7%, of a large number of CH cases, probably reflects the delay in diagnosis. Najjar SS, et al reported that the estimated duration of hypothyroidism was longer in children with the syndrome, particularly in those with more pronounced muscular hypertrophy[6]. This syndrome probably represents the effect of long-standing hypothyroidism on muscles, rather than a peculiar form of hypothyroidism, since no other differences could be found between hypothyroid children with or without muscular hypertrophy. The occurrence of this syndrome in various forms of hypothyroidism and athyreosis, as well as hypothyroidism due to an enzymatic defect in the thyroid hormone synthesis supports this hypothesis.

The results of the thyroid scintigraphy in this study showed that thyroid dysgenesis accounted for the most common etiology (80.9%). This was similar to the previous reports[8-10], and those cases detected by neonatal screening[11-13]. Thyroid ectopy was found to be more common in the cases diagnosed after 24 months of age, but it was also presented in those diagnosed within 3 months after birth. This is contrary to the finding of Seeherunvong T[10], in which no case of ectopic thyroid was reported in this age group. Churesigaew S[9] showed no ectopic thyroid in his study. This may be due to different scintigraphic techniques and thyroid scintigraphy in both studies which were performed after medication had been discontinued for 4-6 weeks. This differed to the present study, in which most of the thyroid scintigraphy was performed before the initiation of medications. The duration of therapy interruption may not be long enough for the full recovery of the pituitary and thyroid glands after long suppression from hormonal treatment.

Not all newborn infants with thyroid dyshormonogenesis have a palpable goiter[8], which is similar to cases in the present study. The palpation of the thyroid in infants is difficult, and it is possible that a goiter had not been searched for carefully enough in every case. Iodine deficiency was ruled out in patient cases 1 and 8 due to the absence of deafness and neuromuscular disorders. Both of

them had recurrent elevation of serum TSH levels and enlargement of the thyroid glands due to poor compliance. Normal maternal thyroid function was detected at the time of diagnosis in patient case 8 and the intelligent quotient performed at age 9 years was 116.

Even low serum T_4 level below 2 μg/dL was found more common in the athyreosis group, but this finding along with elevated serum TSH level and retarded bone age are not helpful in distinguishing among different groups of hypothyroidism.

This will remind physicians to consider the diagnosis of hypothyroidism whenever it is clinically suggested, regardless of whether or not screening is done at birth. All missed cases must be detected as soon as possible.

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โรคพร่องไทรอยด์ฮอร์โมนแต่กำเนิดชนิดปฐมภูมิ: ลักษณะทางคลินิกและสาเหตุ

เกวลี อุณจักร, ประไพ เดชคำรณ

ได้ทำการศึกษาย้อนหลังผู้ป่วยเด็กโรคพร่องไทรอยด์ฮอร์โมนแต่กำเนิดชนิดปฐมภูมิ ในโรงพยาบาลมหาราชเชียงใหม่ตั้งแต่ พ.ศ. 2520-2543 จำนวน 48 ราย อายุตั้งแต่ 1 เดือน ถึง 12 ปี 4 เดือน เป็นเพศหญิง 32 ราย เพศชาย 16 ราย พบผู้ป่วยที่ได้รับการวินิจฉัยภายในอายุ 3 เดือน หรือภายในอายุ 1 ปี หรือหลังอายุ 1 ปี เป็นร้อยละ 27, 37.5 และ 62.5 ตามลำดับ

อาการนำที่พบบ่อย ได้แก่ ท้องผูก พัฒนาการล่าช้า โตช้า ปัญหาการกินอาหาร อาการตัวเหลืองนานในวัยทารก และคอพอก โดยพบอาการตัวเหลืองนานในวัยทารกในผู้ป่วยทุกคนที่ได้รับการวินิจฉัยภายในอายุ 3 เดือน

อาการแสดงที่ตรวจพบตามลำดับได้แก่ ผิวหนังแห้งหรือลาย ท้องโต ลิ้นโต ตัวเตี้ย หน้าบวม และสะดือจุ่น นอกจากนี้ยังตรวจพบกลุ่มอาการ Kocher-Debr -Semelaigne ร้อยละ 18.6 โดยพบเพศหญิง ต่อ เพศชาย ในอัตราส่วน 2:1 และพบในผู้ป่วยที่มีสาเหตุต่าง ๆ ได้ทำการตรวจสแกนต่อมไทรอยด์ผู้ป่วยจำนวน 47 ราย พบสาเหตุจาก thyroid dysgenesis มากที่สุด คือจำนวน 38 ราย คิดเป็นร้อยละ 80.9 โดยตรวจไม่พบต่อมไทรอยด์ ร้อยละ 40.4 ต่อมไทรอยด์ ขนาดเล็ก ร้อยละ 4.3 ต่อมไทรอยด์อยู่ผิดที่ ร้อยละ 36.2 และพบต่อมไทรอยด์อยู่ในตำแหน่งปกติ แต่มีขนาดปกติหรือ ขนาดใหญ่ จำนวน 9 ราย คิดเป็นร้อยละ 18.9 ผู้ป่วยกลุ่มสุดท้ายได้รับการตรวจด้วยวิธี perchlorate discharge test ได้ผลเป็นบวก 6 ราย ซึ่งแสดงว่ามีความบกพร่องในขบวนการสร้างไทรอยด์ฮอร์โมนแบบ organification defect

ผู้ป่วยทุกรายมีระดับ TSH มากกว่า 50 mU/L ผลการตรวจทางห้องปฏิบัติการนี้ ร่วมกับการที่มีระดับ T_4 น้อยกว่า 2 μg/dL และอายุกระดูกล่าช้าไม่สามารถแยกสาเหตุของโรคพร่องไทรอยด์ฮอร์โมนแต่กำเนิดชนิดปฐมภูมิในเด็กได้