Thyroid Functions in Children with Down's Syndrome

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Objective: *To evaluate thyroid function in children with Down's syndrome, and to ascertain the presence of a relationship between overt thyroid diseases and congenital anomalies.*
Material and Method: *One hundred and forty Down's syndrome patients, aged from 3 days to 13 years 9 months, were evaluated for karyotype, thyroid functions and the coexistence of congenital anomalies.*
Results: *Trisomy 21 was found in the majority of cases (95.7%). Fifty-six patients (40%) had abnormal thyroid functions: 53 (37.9%) hypothyroidism and 3 (2.1%) hyperthyroidism. Ten patients (7.1%) were diagnosed with overt thyroid disease: congenital hypothyroidism 3.6%, acquired hypothyroidism associated autoimmune thyroiditis 1.4% and hyperthyroidism 2.1%. None of the patients with congenital hypothyroidism had athyreosis or ectopic thyroid gland. Sub-clinical hypothyroidism accounted for 32.9% of all cases; 10.7% showed a spontaneous decrease to normal TSH levels and 13.6% had persistently elevated TSH levels with the median follow-up time of 6 and 12 months, respectively. Congenital heart disease, gastrointestinal anomalies and hematological disease were found in 73.6, 10 and 3.6 percent of patients, respectively. There was no statistical correlation between the coexistence of cardiovascular or gastrointestinal disease in Down's syndrome patients with overt thyroid diseases or sub-clinical hypothyroidism to those having normal thyroid functions.*
Conclusion: *Sub-clinical hypothyroidism was the most common thyroid abnormality in children with Down's syndrome. A longitudinal and timely-scheduled evaluation of thyroid function is needed to establish the natural course of this abnormality and the proper management guideline.*

Keywords: *Down's syndrome, Abnormal thyroid function, Overt thyroid disease, Congenital hypothyroidism, Acquired hypothyroidism, Hyperthyroidism, Sub-clinical hypothyroidism, Congenital heart disease, Gastrointestinal defect, Hematological disease*

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Down's syndrome (DS) is one of the most common survivable chromosomal syndromes, occurring in one of 600 to 800 live births[1]. DS is more likely to occur with advanced maternal age and has an increased prevalence of autoimmune disorders affecting both endocrine and non-endocrine organs[2]. There is an intriguing association between DS and thyroid abnormalities, which include sub-clinical and overt hypothyroidism, hyperthyroidism, and positive thyroid antibodies. The prevalence of these abnormalities is varied, depending on the diagnostic criteria and the selected population which includes sample size and age group. The prevalence of hypothyroidism in DS is higher than that of hyperthyroidism, and increases with age[3]. The clinical manifestations of hypothyroidism are nonspecific and may be attributed to the DS itself. Diagnosis based solely on clinical features is therefore unreliable, and laboratory findings that confirm diagnosis are essential.

The authors aimed to study the thyroid function in children with DS and examine a relationship between overt thyroid diseases, sub-clinical hypothyroidism and congenital anomalies.

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Material and Method

The present study group comprised 140 children with DS who attended the pediatric clinics of endocrinology, cardiology and genetics at Chiang Mai University Hospital between 1996 and 2002. There were 68 males and 72 females giving the ratio of male to female of 1:1.1. The age at the first visit ranged from 3 days to 13 years 9 months. Eighty-seven patients (62.1%) were under one year of age. All patients had clinical characteristics of DS and confirmed by cytogenetic studies: 134 (95.7%) were trisomy 21, 4 (2.9%) translocation 21/21, and 2 (1.4%) translocation 14/21.

Information on the maternal age at childbirth, the presence of congenital gastrointestinal anomalies, hematological disease, and congenital heart disease were obtained. The latter was confirmed by echocardiography and cardiac catheterization.

Thyroid function tests, which included free thyroxine (FT4) and thyroid stimulating hormone (TSH), were measured at the first and follow-up visit which ranged from 1 month to 6 years. FT4 and TSH were measured by radioimmunoassay (CIS bio international, France) and radio-immunometric assay (CIS bio international, France), respectively. Thyroglobulin and thyroid peroxidase antibodies were measured by the agglutination test (SERODIA-ATG by FUJIREBIO INC.) in patients with abnormal TSH levels. TSH was considered elevated if its level was higher than 20, 10 and 6.5 mU/L in patients aged from newborn to one week, from eight days to one month, and older than one month, respectively. TSH was considered suppressed if its level was lower than 0.4 mU/L. Primary hypothyroidism was recognized from low FT4 and elevated TSH levels, whereas sub-clinical hypothyroidism (SH) was diagnosed by elevated TSH levels only. Hyperthyroidism was diagnosed by high FT4 and suppressed TSH levels. Information of physical findings was obtained in cases of overt thyroid diseases. $A^{99m}Tc$ thyroid scan was performed in patients with congenital hypothyroidism and followed by a perchlorate discharge test in cases of normal size or enlarged gland on thyroid scintigraphy.

Statistical analysis

Wilcoxon Signed ranks test was used for statistical analysis to compare the mean serum TSH level in persistent and transient SH, and $p < 0.05$ was considered to be statistically significant. The odd ratio and Fisher's Exact Tests were used for statistical analysis to compare the coexistence of cardiovascular or gastrointestinal diseases between the DS patients with overt thyroid diseases, sub-clinical hypothyroidism to those with normal thyroid function (Table 2).

The present study was approved by the Ethical Committee of the Faculty of Medicine, Chiang Mai University, Thailand.

Results

Of the 140 DS patients, the maternal age at childbirth was obtained in 127 patients. In this group, 123 were trisomy. The mean maternal age was 31.09 +/- 7.06 years (ranged 14-47). The maternal age of less than 35 years accounted for 62% of DS children with trisomy.

Distribution of 140 patients according to their thyroid function is shown in Fig. 1. Abnormal thyroid function was found in 56 (40%) of 140 DS patients. Ten patients (7.1%), all of whom were diagnosed with overt thyroid diseases, were found to have trisomy 21. Overt thyroid diseases including hyperthyroidism, congenital and acquired hypothyroidism, and their findings are shown in Table 1. Congenital hypothyroidism (CH) was found in five patients reflecting a frequency of 3.6%, and the patients' ages were between 6 days and 2 years. $A^{99m}Tc$ thyroid scan performed in 4 of them showed a normal position, shape and size of the thyroid gland in three and an enlarged gland in one. Neither athyreosis nor thyroid ectopy was found in these patients. During the follow-up time, patients' number 1 and 4 had elevated serum TSH levels up to 22 and 28 mU/L, respectively; therefore central hypothyroidism was excluded.

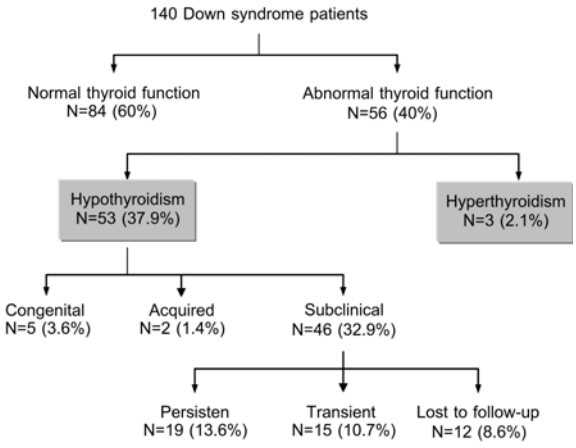

Fig. 1 Distribution of 140 infants and children with Down syndrome according to their thyroid function

Table 1. Findings in DS children with overt thyroid diseases

Case	Age	TSH (mU/L)	FT4 (ng/dL)	^{99m}Tc thyroid scan	Thyroid antibodies	Cardiac defects	Gastrointestinal anomalies
Congenital hypothyroidism							
1	1yr 4m	11	0.4	Normal size	Negative	ASD, VSD	NO
2	6m	20	0.4	Normal size	ND	NO	Imperforate anus
3	6d	170	VL	Normal size, decreased uptake	ND	PDA, ASD	NO
4	2y	11.5	0.6	ND	Negative	ASD	Imperforate anus
5	11d	71	0.5	Enlarged size	ND	PDA	NO
Acquired hypothyroidism							
6	9yr 8m	89.7	0.2	Normal size, decreased uptake	TAT & TPO 1:400	NO	NO
7	10yr	>60	0.5	Enlarged size, 2 cold nodules	TAT 1:100, TPO 1:102,000	NO	NO
Hyperthyroidism							
8	3yr 4m	0.04	3.7	Normal size	TPO 1:400, TAT negative	VSD	NO
9	11yr	0.06	3.7	ND	ND	AVSD	NO
10	7yr 9m	<0.19	2.4	ND	TPO 1:1600, TAT 1:400	Ebstein anomalies	NO

VL: very low, ND: not done, TPO: thyroid peroxidase antibody, TAT: thyroglobulin antibody
ASD: atrial septal defect, VSD: ventricular septal defect, PDA: patent ductus arteriosus, AVSD: atrioventricular septal defect

Table 2. Relationship between congenital anomalies and thyroid function status in children with Down syndrome

Characteristics	Overt thyroid disease (n = 10)	Subclinical hypothyroidism		Normal thyroid function (n = 84)
		Transient (n = 15)	Persistent (n = 19)	
Cardiovascular defects				
Yes	7	10	12	62
No	3	5	7	22
Odd ratio (95% CI)	0.83 (0.19-3.84)	0.71 (0.22-2.3)	0.61 (0.21-1.74)	
p-value	1	0.75	0.4	
Gastrointestinal anomalies				
Yes	2	1	2	11
No	8	14	17	73
Odd ratio (95% CI)	1.6 (0.31-8.85)	0.47 (0.06-3.97)	0.78 (0.16-3.85)	
p-value	0.61	0.68	1	

Two patients (1.4%) had acquired hypothyroidism with positive thyroid peroxidase and thyroglobulin antibodies. Three patients (2.1%) had hyperthyroidism. All presented with weight loss or failure to gain weight, tachycardia, and wide pulse pressure but no goiter. Exophthalmos was noted in one patient.

SH was found in 32.9% of all cases. Fifteen (10.7%) patients showed a spontaneous decrease of TSH to normal levels and 19 (13.6%) patients showed persistently elevated TSH levels with a median follow-up time of 6 and 12 months, respectively. The mean serum TSH levels of the transient group was significantly decreased from 11.48 +/- 9.60 to 0.7 +/- 1.54 mU/L ($p < 0.05$. In contrast to the transient group, TSH levels in the persistent group was not significantly decreased

with follow-up time (13.02 +/- 7.73 vs 10.7 + /- 4.23 mU/L (p 0.33)).

Of the 140 DS children, 103 (73.6%) had congenital heart diseases, and the common lesions were patent ductus arteriosus (35.9%), ventricular septal defect (35.9%), followed by atrioventricular septal defect (24.3%), secondum atrial septal defect (22.3%), tetralogy of Fallot (11.7%), pulmonary stenosis (2.9%), and Ebstein anomalies (1.9%). Forty patients (38.8%) had multiple cardiac defects. Congenital gastrointestinal anomalies were found in 14 patients (10%): seven with imperforated anus, two each with duodenal atresia and Hirschprung disease, and one each with annular pancreas, duodenal stenosis, and malrotation. There were 5 patients (3.6%) with hematological diseases: two with acute myeloblastic leukemia, and one each with b-thalassemia trait, b-thalassemia hemoglobin E, and G-6-PD deficiency.

Of the ten patients with overt thyroid diseases, seven had congenital heart diseases, two had gastrointestinal anomalies, and all were free from hematological diseases. There was no statistically significant difference between the coexistent of cardiovascular or gastrointestinal disease in DS patients with overt thyroid disease or sub-clinical hypothyroidism to those having normal thyroid functions. ($p > 0.05$).

Discussion

The present study showed a relatively high prevalence of congenital heart diseases in children with DS compared to other studies that showed a range from 25-60%[4-6]. Chiang Mai University Hospital was the only referral center for cardiac evaluation in northern Thailand; an echocardiogram is carried out in every DS patient even if no symptoms were present. A normal examination does not exclude heart disease[7]. This may be the reason for the higher prevalence when compared to the study from southern Thailand[8].

Forty percent of abnormal thyroid function provided further evidence of the high prevalence of thyroid dysfunction in DS children, which ranged from 16-60%[3, 9-10]. The higher prevalence when compared to the study from southern Thailand[8] (40% vs.11.4%), may be due to the larger number of patients and the different diagnostic criteria, in which both transient and persistent SH were included in the present study.

In the present study, the prevalence of CH in DS is similar to other studies that ranged from 0.7-6.1%[9-12]. CH was found to be about 28 times more common among newborn with DS than in healthy infant[11], but the etiology of CH in DS children is unclear. Some reports showed athyreosis[9,11,13-14], or an enlarged gland on thyroid scan[11], but most cases had normal position, shape and size of the thyroid[9,11,15-16]. The perchlorate test performed in two of them was positive in one case and negative in another, and thyroid auto-antibodies showed negative results in 2 patients. The etiology of CH could not be verified, due to the inconclusive data.

Two patients aged 9 and 10 years had acquired hypothyroidism with positive thyroid antibodies, which suggested an autoimmune pathogenesis. It is usually found in children aged over 8 years[17] and the prevalence increases with age[3,15,17], but they had a negative correlation between thyroid hormone level and antibodies titer[3]. However, there are two case reports of this condition in DS children aged less than 4 years[9]. The prevalence of thyroid auto-antibodies in an absence of thyroid dysfunction also increases with age[18], and individuals with positive thyroid peroxidase antibodies are expected to have a frequent progression to overt thyroid disease[19].

The frequency of hyperthyroidism was 2.1 percent, which is similar to previous reports that ranged from 0.87-2.5 %[17,20,21]. Hyperthyroidism occurs much less frequently than hypothyroidism in DS cases. It may be under diagnosed, due to a general lack of typical signs or a lack of awareness among physicians.

The prevalence of SH is also similar to several studies[3,16,19,22], which reported 6-44%, and none of the DS children with persistent SH develop an overt hypothyroidism. The natural course of SH in DS is variable. It may show a spontaneous decrease to normal or fluctuating serum TSH levels or developed overt hypothyroidism on follow-up[9,16,19,22].

The pathophysiology of SH is not well understood, may be as a result of inappropriate TSH secretion related to hypothalamic pituitary dysfunction, or thyroid resistance to the level of TSH receptor, or a sign of evolving definite hypothyroidism.

The clinical significance of SH in DS children is also variable; some studies showed no significant difference on growth and development between these children to those with normal thyroid functions[9,17], while Sharav et al found growth retardation in children with DS and SH who were younger than 4 years[10], and Karlsson et al found acceleration of growth after thyroxine treatment[17]. The therapeutic management remains a debatable issue: some endocrinologists recommend retesting in 3-6 months later, while others suggests treatment. In those identified with SH, the authors suggest follow up and retesting more frequently

than the guideline of the American Academy of Pediatrics[23] to establish a natural course and proper management. Early detection and prompt treatment of hypothyroidism could contribute to better intellectual and developmental outcomes.

In contrast to the previous study[4] which showed the correlation between congenital gastrointestinal anomalies and hypothyroidism in DS children, the present study could not identify the correlation between any congenital anomalies and overt thyroid diseases or sub-clinical hypothyroidism. However, the number of patients with congenital cardiac diseases seems to be more frequently found in DS children with overt thyroid diseases.

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การทำงานของต่อมไทรอยด์ในเด็กกลุ่มอาการดาวน์

เกวลี อุณจักร, ประนุท ตันไพบูลย์, ยุพดา พงษ์พรต, แรกขวัญ สิทธิวังกูร, สุชยา ศิลป์ไวไลรัตน์, ประไพ เดชคำรณ, จุทามาศ สุทัศน์

วัตถุประสงค์*: เพื่อศึกษาการทำงานของต่อมไทรอยด์ในผู้ป่วยเด็กกลุ่มอาการดาวน์ที่มารับการรักษาที่โรงพยาบาลมหาราชนครเชียงใหม่ และศึกษาความสัมพันธ์ระหว่าง overt thyroid disease กับความผิดปกติแต่กำเนิด*

วัสดุและวิธีการ*: ทำการตรวจคาริโอไทพ์ การทำงานของต่อมไทรอยด์ (free T4 & TSH) และประเมินความผิดปกติแต่กำเนิดในผู้ป่วยกลุ่มอาการดาวน์ จำนวน 140 คน อายุ 3 วัน ถึง 13 ปี 9 เดือน*

ผลการศึกษา*: ความผิดปกติของคาริโอไทพ์ที่พบบ่อยที่สุดคือ trisomy 21 และมีการทำงานต่อมไทรอยด์ผิดปกติร้อยละ 40 โดยเป็นภาวะพร่องไทรอยด์ฮอร์โมน ร้อยละ 37.9 ภาวะต่อมไทรอยด์ทำงานเกิน ร้อยละ 2.1 หรือแยกเป็น subclinical hypothyroidism ร้อยละ 32.9 และ overt thyroid disease ร้อยละ 7.1 โดยแบ่งเป็นภาวะพร่องไทรอยด์ฮอร์โมนแต่กำเนิด ร้อยละ 3.6 ภาวะพร่องไทรอยด์ฮอร์โมนจากต่อมไทรอยด์อักเสบ ร้อยละ 1.4 และภาวะต่อมไทรอยด์ทำงานเกินร้อยละ 2.1 ในกลุ่มพร่องไทรอยด์ฮอร์โมนแต่กำเนิดไม่พบสาเหตุจากการไม่มีต่อมไทรอยด์หรือมีอยู่ในตำแหน่งที่ผิดปกติ พบโรคหัวใจแต่กำเนิด โรคทางเดินอาหาร และโรคเลือด ร้อยละ 73.6, 10 และ 3.6 ตามลำดับ กลุ่ม subclinical hypothyroidism ร้อยละ 10.7 มีระดับ TSH ลดลงเป็นปกติ และร้อยละ 13.6 ยังคงมี TSH สูง เมื่อติดตามผู้ป่วยเป็นระยะเวลา 6 และ 12 เดือนตามลำดับ ไม่พบความสัมพันธ์ระหว่างการที่มีโรคหัวใจแต่กำเนิดหรือโรคทางเดินอาหารกับ overt thyroid disease และ subclinical hypothyroidism*

สรุป*: ในเด็กกลุ่มอาการดาวน์ พบการทำงานของต่อมไทรอยด์ที่ผิดปกติชนิด subclinical hypothyroidism บ่อยที่สุด ควรมีการประเมินการทำงานของต่อมไทรอยด์อย่างต่อเนื่อง เพื่อให้ทราบถึงการดำเนินโรค และให้แนวทางในการรักษาที่เหมาะสม*