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Thyroid Dysfunction in Chinese Children and Adolescents with Down Syndrome

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Abstract

Objective: To document the occurrence of thyroid dysfunction in Chinese children and adolescents with Down syndrome. **Method:** Four hundred and sixteen Chinese children and adolescents with Down syndrome were studied retrospectively for thyroid dysfunction. Hospital records from seven regional hospitals were reviewed. Records could not be traced in 65 of them. Among the 351 subjects, 200 were boys while 151 were girls. The age ranged from 0 to 18.99 years. **Results:** Thyroid function was normal in 250 patients (71.2%). Seven patients had congenital hypothyroidism (2.0%), seven had acquired hypothyroidism (2.0%) and seventy-nine had subclinical hypothyroidism (22.5%). Hyperthyroidism was found in 8 of them (2.3%). Serum thyroid stimulating hormone (TSH) or free thyroxine (fT4) level could be traced in 200 of them. There was no significant difference in mean fT4 levels between the normal group (118 patients) and the group with subclinical hypothyroidism (70 patients). Patients with subclinical hypothyroidism were subdivided into two groups: G1 (n=61) with TSH=5-10 mIU/L and G2 (n=9) with TSH>10 mIU/L. There was no significant difference in fT4 levels between the two groups. Sixty-seven patients had been screened for auto-antibodies. Anti-thyroglobulin antibodies and/or anti-thyroid microsomal antibodies were found in 25 patients. All 8 patients with hyperthyroidism were positive in either one or both autoantibodies. Two out of 6 patients with acquired hypothyroidism and 10 out of 29 with subclinical hypothyroidism had positive autoantibodies while thyroid autoantibodies were present in 5 out of 20 patients with normal thyroid function. **Conclusion:** Thyroid dysfunction is very common in patients with Down syndrome. Regular blood test for thyroid function is recommended. The fT4 levels of subclinical hypothyroidism did not differ significantly from the normal group. Further study is required to support the need for treatment in these patients. The presence of thyroid autoantibodies in all patients with hyperthyroidism highly suggests an autoimmune origin.

Key words Down syndrome; Thyroid autoimmunity; Thyroid dysfunction

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Introduction

Down syndrome (DS) is a well known chromosomal disorder that has a high association with endocrine disease. The most common one is thyroid dysfunction. Congenital hypothyroidism was found to be almost 28 times more frequent than the general population.[1] Most patients have normal thyroid scans, excluding athyreosis or ectopic thyroid.[1,2] Loudon and co-workers had found that out of 116 DS children, 3 had acquired hypothyroidism, 2 had compensated hypothyroidism and 1 had hyperthyroidism.[3] Karlsson reported hypothyroidism in 28 out of 85 DS children while hyperthyroidism was found in two.[4] Clinical diagnosis of hypothyroidism is difficult in DS. The hypothyroid features can be masked by the phenotypic appearance and symptoms such as weight gain and poor growth might be attributed to the syndrome itself.[5] Thus, routine thyroid function screening is important for all children with Down syndrome.[4]

An autoimmune aetiology has been suggested because of the association with autoimmune disease and the presence of anti-thyroglobulin antibody (ATA) and anti-microsomal antibody (AMA). The reported prevalence of thyroid autoantibodies is 13-34% in patients with DS[4] and it increased with age as it did in the general population.[4,6] Acquired hypothyroidism was found in 1 out of 49 patients with the presence of thyroid anti-microsomal antibody and anti-thyroglobulin antibody.[2] In another study, autoimmune antibodies were found in 47 out of 151 DS patients aged from 3 to 21 years. However, only 19 of them had abnormal thyroid stimulating hormone (TSH) and/or free thyroxine (fT4) levels.[7]

We studied children and adolescents with Down syndrome in our locality for the prevalence of thyroid disorder and the incidence of autoantibodies as well as their relationship with thyroid dysfunction.

Methods

Hospital records of Down syndrome patients between 1986 and 2001 from Department of Paediatrics of 7 regional hospitals in Hong Kong were reviewed by Paediatricians. Information was recorded in the form of a questionnaire. In this study, data concerning the diagnosis, age and thyroid function tests (TFT) at onset of thyroid disorder, antibody status and symptoms, if any, as well as investigation results were retrieved.

Three hundred and fifty-one patients were included into the study based on the documentation of diagnoses in the hospital records. In fact, all patients have TFT checked but the numerical data concerning the TFT could not be traced in some hand written records. As a result, only 200 data were included in the analysis of thyroid functions.

Either verbal or written consent were obtained from parents of the subjects. Serum TSH and fT4 were measured by routine in-house methods. The methods of assay had been changed a couple of times in the past decade. Furthermore, the methods varied among different regional hospitals as well as the range of normal references (Table 1). Yet the

Table 1 Methods of assay and different reference ranges among different regional hospitals

Hospitals	Methods of assay	TSH (mIU/L)	fT4 (pmol/L)
QEH	Radioimmunoassay (86-92)	0.3-4.0	8.5-20.7
	Chemiluminescence immunoassay (92-00)	0.35-5.5	11.5-23.2
	Electrochemiluminescence immunoassay (00-01)	0.27-4.2	12.0-22.0
PYNEH	Microparticle enzyme immunoassay (93-99)	0.32-5.0	9.1-23.8
	Chemiluminescent microparticle immunoassay (99-01)		
PMH	Chemiluminescent immunoassay	0.3-3.0	9.0-23.0
TMH	Immunoassay ROCHE E170	0.27-4.2	13.0-23.0
CMC	Microparticle enzyme immunoassay	0.5-4.7	9.1-23.8
AHNH	Electrochemiluminescence immunoassay	0.8-6.46	12.1-22.0
PWH	Immunomatric assay for TSH analysis	0.3-4.2	12.0-22.0
	Analogue assay for fT4 analysis		

difference was very small. Total T4 and free T3 were measured in some regional hospitals instead of fT4 and the data were not included in the analysis. Serum anti-thyroglobulin antibody (ATG) and anti-microsomal antibody (AMA) were also measured.

Universal screening of cord blood TSH has been started since 1983 in Hong Kong. It allows early detection of congenital hypothyroidism which is of great importance to prevent impairment of the neurodevelopment in DS patients as well as normal children. Congenital hypothyroidism was suspected if cord blood TSH level was above 15 mIU/L. Thyroid function would be rechecked on day 5 of life. Congenital hypothyroidism was diagnosed if TSH was raised above normal and fT4 level was below normal limit. Thyroid scan would be performed for the detection of any functioning thyroid in the normal anatomical position. Subclinical hypothyroidism was diagnosed if serum TSH was equal or above 5 mIU/L while fT4 levels remained normal. It was further subdivided into two groups: G1 (n=61) with TSH=5-10 mIU/L and G2 (n=9) with TSH >10 mIU/L. In acquired hypothyroidism, serum TSH level was greater than 5 mIU/L and at the same time the serum fT4 was below normal limit. Hyperthyroidism was diagnosed if serum fT4 was above normal and a serum TSH below normal.

Data were analysed by Statistical Package for the Social Sciences (SPSS, Window version 11.0) software. Fisher's exact test was used to compare the categorical variables and $p<0.05$ was considered to be statistically significant.

Results

In the 422 DS patients recruited, six of them were excluded because they were non-Chinese. Records could only be traced in 351 patients (Figure 1). There were 200 males and 151 females whose ages ranged from 0 to 18.99 years old. Thyroid dysfunction was found in 101 (28.8%) patients while 250 (71.2%) of them had normal thyroid function. There were 7 (2%) patients with congenital hypothyroidism, 7 (2%) with acquired hypothyroidism, 79 (22.5%) with subclinical hypothyroidism and 8 (2.3%) with hyperthyroidism. There was no difference in sex distribution in each diagnosis (Table 2).

Congenital hypothyroidism was found in seven patients. Thyroid scan had been performed in six of them and results could be traced in only five subjects. The scan results were all normal.

In our study, the most common thyroid disorder was subclinical hypothyroidism. It was found that more than half of the patients with hypothyroidism including both subclinical and acquired hypothyroidism were diagnosed before 5 years old and the frequency reduced with age (Table 3, Figure 2). The mean age at diagnosis for acquired hypothyroidism was 5.4±4.7 years old, ranged from 1.5 to 14.3 years of age while the mean age at diagnosis for subclinical hypothyroidism was 4.9±4.4 years old, ranged from less than 1 month to 18.9 years of age. In contrary, hyperthyroidism was more common in older patients and

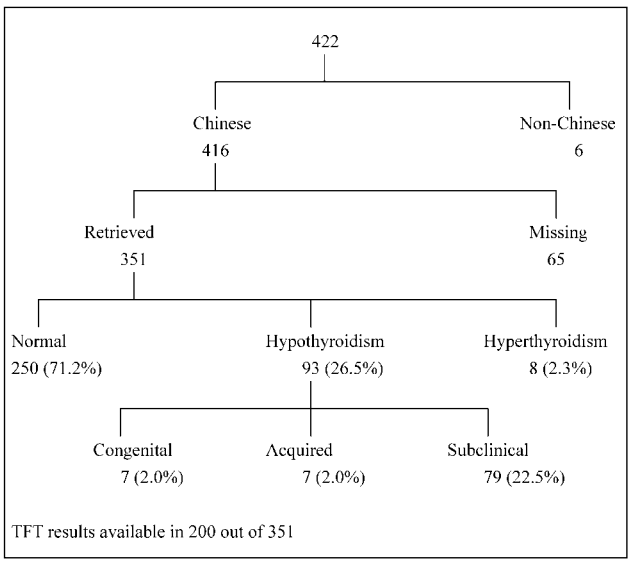

Figure 1 Distribution of the studied subjects according to the diagnosis.

Table 2 Prevalence of thyroid disorder and sex distribution

	Male	Female	Frequency	Percentage
Normal	144	106	250	71.2
Congenital hypothyroidism	5	2	7	2.0
Acquired hypothyroidism	3	4	7	2.0
Subclinical hypothyroidism	45	34	79	22.5
Hyperthyroidism	3	5	8	2.3
Total	200	151	351	100.0

the mean age at diagnosis was 11.8±3.6 years old, ranged from 7.6 to 18.1 years of age (Table 4).

For the analysis of thyroid function tests including TSH and fT4, data were missing in 151 of them. Patients with subclinical hypothyroidism were further subdivided into two groups according to the TSH values. Group 1 (G1) consisted of 61 patients with TSH value 5-10 mIU/L while group 2 (G2) consisted of 9 patients with TSH value above 10 mIU/L. Nine patients were not included in the subdivision because of missing data on thyroid function test. The mean fT4 level was 15.7±2.7 pmol/L for normal while the mean fT4 was 16.0±2.5 pmol/L for G1 and 16.2±4.8 pmol/L for G2. There was no significant difference in the mean fT4 levels between the normal group (n=118) and the group with subclinical hypothyroidism (n=70) with a p-value of 0.564. Again, there was no significant difference in the values of fT4 between the two subgroups in subclinical hypothyroidism with a p-value of 0.919 (Table 4). The mean fT4 level for acquired hypothyroidism was 11.1 pmol/L and was significantly lower when compared with that of the normal and the group with subclinical hypothyroidism.

Anti-thyroglobulin antibody or anti-microsomal antibody results were available in 67 subjects. Either or both antibodies were found in 25 patients (37%). Five of them had normal thyroid functions. Two of them had acquired hypothyroidism while 10 had subclinical hypothyroidism. All eight patients with hyperthyroidism had at least one antibody (Table 4). It was found that the incidence of autoantibodies was significantly higher for those with onset at 8 years old or above than those with onset below 8 (p=0.032) (Table 5).

Discussion

Thyroid dysfunction, especially hypothyroidism is very common in Down syndrome. An autoimmune aetiology has been suggested based on an increased frequency of thyroid autoantibodies in DS.[5,8,9]

The prevalence of thyroid disorder in DS patients of our study was 101 in 351 (28.8%). Seven out of 351 (2.0% or 1 in 50) DS patients had congenital hypothyroidism which

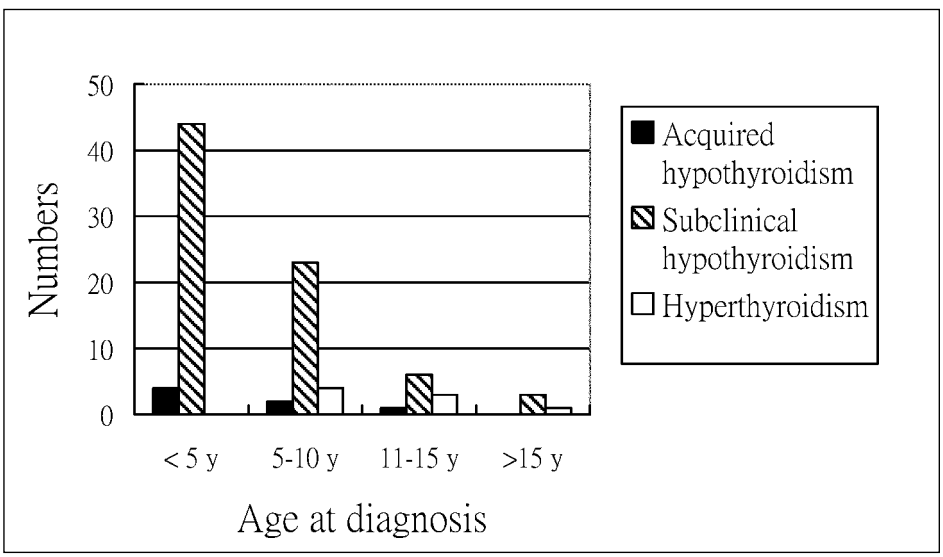

Figure 2 Distribution of age at diagnosis.

Table 3 Distribution of age at diagnosis

	No. of patients (%)				
Age (yr)	**<5**	**5-10**	**11-15**	**>15**	**Total**
Acquired hypothyroidism	4 (57.1)	2 (28.6)	1 (14.3)	0	7
Subclinical hypothyroidism	44 (57.9)	23 (30.3)	6 (7.9)	3 (3.9)	76*
Hyperthyroidism	0 (0)	4 (50)	3 (37.5)	1 (12.5)	8

*Data of age at diagnosis in 3 patients with subclinical hypothyroidism were not available

Table 4 Thyroid function tests at diagnosis and antibody results

Thyroid status	Sex M/F	No.* 200/342	Age at diagnosis	TSH (mIU/L)	fT4 (pmol/L)	Antibody present No. (%)	Median ATG (range)	Median ATM (range)
Normal	M F	66/144 52/106	6.8±4.8	2.91±1.06	15.8±2.7	5/20 (25%)	99.5 (99-100)	99.0
Congenital hypothyroidism	M F	4/5 0/2	0.1±0.2	43.55±27.57	15.1±3.3	0/4 (0%)		
Acquired hypothyroidism	M F	0/3 1/4	5.4±4.7	11.81	11.1	2/6 (33.3%)	90 (80-100)	4000 (1600-6400)
Subclinical hypothyroidism G1	M F	33/33 28/28	4.6±4.5	6.58±1.38	16.0±2.5	8/24 (33.3%)	99 (99-2560)	99 (99-2560)
Subclinical hypothyroidism G2	M F	5/5 4/4	4.1±3.2	12.64±1.76	16.2±4.8	2/5 (40%)	100	100
Hyperthyroidism	M F	3/3 4/5	11.8±3.6	0.02±0.01	45.9±16.2	8/8 (100%)	400 (100-102400)	64000 (1600-102400)

*TFTs were available in 200/342 subjects; 9 subjects with subclinical hypothyroidism were not categorised into subgroups because of missing TFTs; G1- TSH 5-10 mIU/L; G2- TSH >10 mIU/L; $p<0.05$ with comparison to normal groups; antibody screened in 67 subjects.

Table 5 Relationship between incidence of autoantibodies and age of onset at diagnosis of thyroid dysfunction excluding congenital hypothyroidism

Age	No. of patients		Incidence of antibody
	Presence of antibody	Absence of antibody	
Onset <8 years	9	18	33.3%
Onset ≥8 years	11	5	68.8%
Total	20	23	46.5%

P=0.0316 by Fisher's Exact Test

was comparable to the study of Fort[1] and Tüysüz[10]. Fort et al reported congenital hypothyroidism in 12 out of 1130 DS patients (1.1% or 1 in 94), which was 28 times greater than normal population.[1] Cutler et al reported a prevalence of 6% (3 out of 49)[2] while Tüysüz reported a prevalence of 1.8% (6 out of 320).[10] The aetiology for congenital hypothyroidism in DS patients is still unclear but does not appear to be due to autoimmune diseases since antibodies were not detected in these patients.[1,11] It had been suggested that maternal autoantibodies could predispose to a chromosomal abnormality. However, there is little evidence to support this hypothesis.[12] Macroscopic thyroid gland extension with histologically increased collagen formation and fibrosis was shown in an autopsy review and thus an embryological developmental defect leading to hormonal dysfunction had been suggested.[13] Recently, it has been concluded that thyroid formation depends on some transcription factors which promote migration as well as differentiation of thyroid cells and action of which is exerted during fetal development. Impairment of these factors is often associated with agenesis or hypoplasia of the thyroid gland.[14]

Excluding congenital hypothyroidism, there were 86 out of 351 (24.5%) DS patients with hypothyroidism, of which, 79 (22.5%) were subclinical and 7 (2%) were acquired. However, the uncertain thyroid function test results in 9 patients of subclinical hypothyroidism and 6 patients of acquired hypothyroidism made us difficult to conclude on the actual prevalence. Prevalence of hyperthyroidism was 8 out of 351 (2.3%). Subclinical hypothyroidism represented more than three quarters of thyroid disorders (79/101) in DS patients. Cutler et al reported 27% (13 of 49) of DS children having compensated hypothyroidism and only 1 patient with hyperthyroidism.[2] Loudon et al reported 5 (4.3%) hypothyroidism, (3 acquired and 2 subclinical) and 1 (0.9%) hyperthyroidism out of 116 DS children.[3] In a study of 160 adult patients with DS, Prasher reported subclinical hypothyroidism in 12% of patients, acquired hypothyroidism 8% and hyperthyroidism 3%.[12] In another study of 320 DS children between 5 days and 10 years old, Tüysüz and Beker reported one (0.3%) acquired hypothyroidism, 81 (25.3%) subclinical hypothyroidism and none hyperthyroidism.[10] The variability of the reported prevalence could be explained by the difference in sample

size, the variation in age groups of the subjects and the diverse approaches in the identification of hypothyroidism. Autoimmune hyperthyroidism was more common than autoimmune hypothyroidism in our study. It had been reported that childhood Graves' disease was common in Hong Kong and its incidence appeared to be higher than those reported in Caucasian children.[15,16] The exact reasons for the high incidence of autoimmune hyperthyroidism in the local population remain unclear. The results of different studies compared with our study are shown in Table 6.

Controversy exists about the pathogenesis of hypothyroidism in infants and young patients with DS. Secretion of biologically less active TSH had been proposed. However, TSH was found biologically normal in a study and defects in signal transduction pathways of thyroid hormonogenesis was postulated to explain the aetiology of subclinical hypothyroidism in patients with DS.[8,17] Others suggested that some degree of thyroid hypofunction was responsible for the mildly elevated TSH level found in patients with DS. Although anti-thyroid antibodies were more prevalent in DS patients than in the general population, this autoimmunity did not seem to impair thyroid function in young patients.[4,18]

The fT4 levels of subclinical hypothyroidism, including both G1 (5-10) and G2 (>10) subgroups in our study did not differ significantly from the normal group. However, their growth parameters and the effects of thyroxine replacement were not studied. It is still controversial whether thyroxine replacement will improve growth in DS patients with mildly elevated TSH.[6,18,19] Study by Sharav et al had showed improvement in the abnormal growth in DS patients with subclinical hypothyroidism[19] while the study by Gruiñero de Papendieck et al failed to demonstrate this effect.[18] Further study is required to support the need for treatment in these patients. In general, treatment with L-thyroxine is recommended in patients with overt hypothyroidism. Euthyroid patients with mildly raised TSH (not greater than 10 mIU/L) or the presence of antibodies does not usually warrant treatment.[20-22]

In our study, 37% (25 out of 67) of DS patients had at least one antibody. Among those positive for thyroid antibodies, 5 out of 20 were euthyroid. Two out of 6 had acquired hypothyroidism, 10 out of 29 had subclinical hypothyroidism while 8 out of 8 had hyperthyroidism. Loudon reported 29% of DS patients had at least one thyroid antibody in a study of 116 DS children. This was much higher than the general population.[3] Pueschel and Pezzullo reported that 31% of DS patients had elevated thyroid antibodies.[7] Ivarsson et al found that as high as 39% of DS children and adolescence were positive for thyroid antibodies.[23] The incidence of thyroid antibody in our group of patients was very probably comparable to other previous studies (Table 7). However, there was no conclusion on the overall incidence of thyroid antibodies in DS children and adolescents in this study due to the reason that antibody status was not known in a large proportion of patients. Antibody screening had only been done in 1/5 (67 out of 351) of the DS patients.

Table 6 Comparison of results of different studies with our study

	Karlsson[4]	**Loudon[3]**	**Cutler[2]**	**Fort[1]**	**Gruiñero de Papendieck[18]**	**Tüysüz[10]**	**Our study**
No. of subjects	85	116	49	1130	137	320	351
Age (yr)	1-25	0.75-19.83	0.33-3	newborn	0.04-16	0-10	0-18.99
Normal	55 (64.7%)	110 (96.6%)	31 (63.3%)	1118 (98.9%)	68 (49.6%)	230 (71.9%)	250 (71.2%)
Congenital hypothyroidism	0 (0%)	0 (0%)	3 (6.1%)	12 (1.1%)	4 (2.9%)	6 (1.8%)	7 (2.0%)
Acquired hypothyroidism	28 (32.9%)	3 (2.6%)	1 (2.0%)	-	8 (5.8%)	1 (0.3%)	7 (2.0%)
Subclinical hypothyroidism	0 (0%)	2 (1.7%)	13 (26.5%)	-	53 (38.7%)	81 (25.3%)	79 (22.5%)
Hyperthyroidism	2 (2.4%)	1 (0.9%)	1 (2.0%)	-	4 (2.9%)	0 (0%)	8 (2.3%)

Table 7 Comparison of incidence of autoantibodies with different studies

	Loudon[3]	Pueschel[7]	Ivarsson[23]	Our study
No. of subjects	116	151	70	351
No. screened (%)	95 (81%)	151 (100%)	70 (100%)	67 (19%)
ATG	8	19	25	21
AMA/APA	26	42	22	25
Incidence of antibodies (%)	28 (29%)	47 (31%)	27 (39%)	25 (37%)

ATG: anti-thyroglobulin antibody; AMA: anti-microsomal antibody; APA: anti-peroxidase antibody

DS patients with circulating autoantibodies may have hypothyroidism, hyperthyroidism or normal thyroid function. On the other hand, not all individuals with clinical thyroid disease have autoantibodies.[2] Karlsson reported that half of the patients developed hypothyroidism at a young age (14 of 28) and only one out of the 11 children tested had detectable thyroid peroxidase autoantibody (TPO) and none were positive for thyroglobulin autoantibodies (ATG). For those with onset after the age of 8 years, 11 of 13 children tested were positive for one or both autoantibodies. It was concluded that autoimmune thyroid disease was uncommon in young children with DS but was common after 8 years old.[4] In our study, the incidence of thyroid antibodies (ATG & AMA) in patients with onset of hypothyroidism before 8 years of age was 33.3% (9 in 27) while that with onset after 8 years of age was 68.8% (11 in 16). The difference was statistically significant (p=0.0316). Autoimmune thyroid disease appeared more common in children with DS after 8 years of age. Nevertheless, anti-thyroid antibodies were present in all patients with hyperthyroidism and it highly suggested an autoimmune origin. Screening for thyroid autoantibodies enables us to identify those patients with higher risk of developing hyperthyroidism or converting from subclinical to autoimmune overt hypothyroidism.

Signs and symptoms of hypothyroidism are easily masked by the phenotypic features of Down syndrome. In addition, there is a poor correlation between clinical hypothyroidism and biochemical hypothyroidism.[12] This makes screening of thyroid function essential in DS patients. In our study, majority of the patients were asymptomatic, though the results were not presented. This was not surprising since most of them were non-complaining. Constipation was the most common symptom (12 patients). However, 7 of them were euthyroid, 1 had congenital hypothyroidism, 3 had subclinical hypothyroidism while 1 had hyperthyroidism. This again suggested a poor correlation between hypothyroidism and clinical symptoms in DS patients. Goitre was present in 2 patients who were hyperthyroid. Tremor and weight loss were also reported in one patient with hyperthyroidism. Though there was no complaint of growth delay in our patients, retarded growth had been reported in DS children with high serum TSH levels compared with those with normal TSH levels independent of thyroxine levels.[19]

Regular screening of thyroid function at yearly intervals has been recommended after the recognition of difficulty in clinical detection of thyroid disorders (especially hypothyroidism) in these patients.[5,7,9,10,12] This can ensure early detection of thyroid problem and eliminate its negative contribution to the neurodevelopment and growth of these children, thereby optimising their potential. Thyroid function should be tested more frequently in euthyroid patients with mildly raised TSH (not greater than 10 mIU/L) or the presence of antibodies as they are at increased risk of developing overt hypothyroidism. In addition, blood testing for thyroid function should be performed at times between regular screenings in the presence of symptoms of thyroid dysfunction.

Our study is a retrospective study and there are many limitations in the data collection. Firstly, many data of thyroid functions were incomplete and the diagnosis of thyroid dysfunction could not be verified. Secondly, the data were collected from seven regional hospitals. The strategies for investigation of thyroid disorders, the methods used to determine thyroid function and the reference ranges vary slightly in different hospitals. Nevertheless, longitudinal follow up can provide more understanding of thyroid dysfunction and impact of thyroid autoimmunity on the development and progression of thyroid disease among these children. Hopefully, this can lead to the accomplishment of a standardised approach for thyroid disorders in children with Down syndrome. Besides, the association with many medical and psychosocial problems

in Down syndrome signifies the importance of a multi-disciplinary management. A close coordination among different specialists will definitely improve the quality of lives in these patients and their families.

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