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Thyroid Dysfunction in Chinese Children with Down Syndrome

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Abstract Thyroid dysfunction, especially primary hypothyroidism, is common among patients with Down Syndrome. The clinical features of hypothyroidism cannot be easily distinguished from those of Down syndrome and a screening programme is necessary for early detection. This study showed that the prevalence of primary hypothyroidism was 33% among boys and 31% in girls while the prevalences of thyrotoxicosis and Hashimoto thyroiditis was each at 1.3%.

Key words Chinese; Congenital hypothyroidism; Down syndrome; Primary hypothyroidism

Introduction

Down syndrome (DS) is one of the most common chromosomal disorders (about 1 in 800 births) and a common cause for mental retardation. It is well recognised that patients with DS have increased prevalence of thyroid dysfunction.[1,2] Primary hypothyroidism (PH), which is defined as elevated thyroid-stimulating hormone (TSH) level,[3] is the most common thyroid disorders in DS.[4] It could be either compensated, i.e. with normal serum free thyroxine (T4) level or decompensated, i.e. with sub-normal free T4 level. Friedman et al showed that 20.3% of patients with DS had previously unrecognised hypothyroidism.[5] Although less common than PH, hyperthyroidism is also more common in DS than in the general population and that 1.4% of children with DS had thyrotoxicosis.[5] In addition, the incidence of congenital hypothyroidism (CH) is also higher than the general population. Fort et al reported 12 cases of CH out of 1130 infants of DS with an incidence of 1:141 compared to 1:3800 in the general population.[6]

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The exact aetiology for the thyroid dysfunction is unknown, although the glands of the majority of patients with DS showed increased colloid formation or fibrosis.[7]

Symptoms of hypothyroidism e.g. stunted growth velocity, weight gain, etc., may not be easily distinguished from the features of DS. As the patients have already had impaired growth and learning disability, it is essential to detect hypothyroidism early so as to avoid further disability. There was a report on cases of pericardial effusion as a presenting feature of PH.[8] Therefore, early detection by screening is essential and has been included in many follow up programmes for patients with DS.[9]

In this study, we aimed at estimation of prevalence of thyroid disease in DS in the local Chinese population from infancy to late adolescence. We performed thyrotrophin-releasing hormone (TRH) stimulation test in those <1 year old to further delineate whether an infant had a hypothyroid state requiring treatment.

Methods

Since May 1997, a comprehensive screening programme for patients with DS has been initiated in the Department of Paediatrics of our Hospital.

Ninety-two patients with DS (56 males, 36 females) attended our clinic for DS. Seventy-eight patients (84%) attended follow-ups during the period under review. There were 52 males and 26 females. The age ranged from 0.2 to

18.5 years. The first thyroid function test results during visits were collected. The patients were divided into 4 groups according to age in order to compare the prevalences of thyroid dysfunction in different age groups. Group 1 was from newborn to 1.0 year old. Group 2 was from 1.1 to 5.0 years old. Group 3 was from 5.1 to 10.0 years old and Group 4 was from 10.1 to 18.5 years old.

Serum concentrations of TSH and free T4 were measured using electrochemiluminescence immunoassay (Roche Elecsys 2010, Roche Diagnostics, Germany). The reference range for TSH and free T4 were 0.27-4.2 mIU/L and 13-23 pmol/L respectively. PH was diagnosed when TSH was above the upper limit of normal. If the serum free T4 level is within the normal range, the PH was compensated. If the serum free T4 was below the normal range, then the PH was decompensated. Thyrotoxicosis was diagnosed when TSH level was below the lower limit of normal and free T4 level was above the upper limit of normal. Anti-microsomal antibody was measured by haemagglutination kit for semi-quantitative measurement (Thymune-M, Murex) and the result was positive with titre of 1:100 or above. Anti-thyroglobulin antibody was measured by haemagglutination kit for detection of thyroglobulin antibody (Thymune-T, Murex) and the result was positive with titre of 1:10 or above. Owing to the retrospective nature of our study, not all patients would have their free T4 levels checked. Likewise, anti-microsomal and anti-thyroglobulin antibodies were performed in some of the patients only.

For infants less than 1 year of age, TRH stimulation tests were performed when basal TSH levels were raised. If peak TSH levels were greater than 30 mIU/L,[3] PH was confirmed. Blood was sent for anti-microsomal and anti-thyroglobulin antibodies and thyroid scintiscan was carried out.

The proportion of PH for all the DS population and each group and each sex were calculated with 95% confidence interval in brackets.

Results

Group 1 comprised 12 infants. Four male and 4 female infants had normal TSH levels. The other 4 infants, all males (no statistically significant difference between male and females), had raised basal TSH levels (Table 1). In 3 of

Table 1 Results of thyroid function tests in 25 children with Down Syndrome and Primary Hypothyroidism

	Patient	Sex	Age (year)	TSH (mIU/L)	Free T4 (pmol/L)	TSHp (mIU/L)	AMA	ATA
Group 1	1	M	0.42	8.68	14.9	49.6	-ve	-ve
	2	M	0.49	11.17	12.6	58.6	-ve	-ve
	3	M	0.54	19.5	17.4		-ve	-ve
	4	M	0.85	5.89	14.5	54.8	-ve	-ve
Group 2	5	F	1.41	7.67	16.4		-ve	-ve
	6	F	2.21	5.53	16.1			
	7	F	2.25	8.04	17.8		-ve	-ve
	8	M	2.45	5.8	17.2		-ve	-ve
	9*	F	3.22	4.55			-ve	-ve
	10	M	3.81	4.49	17.5		-ve	-ve
Group 3	11	M	5.29	5.39	15.0			
	12	M	5.34	5.48	18.3		-ve	-ve
	13	F	5.37	12.06	18.9			
	14*	M	5.42	4.37				
	15	M	5.46	5.69	17.0			
	16	M	6.07	21.5	13.7	81.0	1:6400	1:80
	17	M	6.5	4.67	15.5		-ve	-ve
	18	F	7.0	9.48	14.5		-ve	-ve
	19	M	7.73	9.13	15.6			
	20*	F	8.57	4.88				
	21	M	9.23	15.49	17.8		-ve	-ve
Group 4	22*	M	10.71	4.21			1:400	-ve
	23*	M	15.5	4.88				
	24*	M	15.69	4.26				
	25*	F	18.56	4.38				

Sex: M=male, F=female; TSHp: peak TSH after TRH stimulation; AMA: anti-microsomal antibody titre, -ve: negative; ATA: anti-thyroglobulin antibody titre, -ve: negative

*free T4 level not checked in first blood taking

them, the basal TSH ranged from 5.89 to 11.17 mIU/L and free T4 ranged from 12.6 to 14.9 pmol/L. The peak TSH levels after TRH stimulation tests were from 49.6 to 58.6 mIU/L. These 3 infants had no symptoms suggestive of hypothyroidism. In the fourth infant, the basal TSH was 19.5 mIU/L and the free T4 was 17.4 pmol/L and clinically he had constipation. TRH stimulation test was not performed because of parental refusal. However, he was at risk of developing further impairment in neuro-development as a result of his hypothyroid state.[10] All 4 patients had normal thyroid scintiscan and were negative for anti-microsomal and anti-thyroglobulin antibodies. Thyroxine treatment was started in these 4 patients.

Group 2 consisted of 15 males and 11 females. There were 2 males and 4 females found to have compensated PH with TSH from 4.49 to 8.04 mIU/L and free T4 levels from 16.1 to 17.8 pmol/L (Table 1). None of them had symptoms of hypothyroidism and no treatment was started. One girl, aged 4.7 years, had biochemical evidence of thyrotoxicosis with basal TSH and free T4 levels at <0.05 mIU/L and 46.0 pmol/L respectively. Both anti-microsomal and anti-thyroglobulin antibodies were negative. Although she had no symptoms suggestive of thyrotoxicosis, carbimazole was started to control her thyrotoxic state.

Group 3 consisted of 20 males and 7 females. There were 8 males and 3 females having compensated PH with TSH ranged from 4.37 to 21.5 mIU/L and free T4 from 13.7 to 18.9 pmol/L (Table 1). Thyroxine was not started in these patients except for a 6.07 year-old boy having basal TSH and free T4 at 21.5 mIU/L and 13.7 pmol/L respectively. Clinically he had decrease in activity level. Anti-microsomal and anti-thyroglobulin antibody titres were 1:6400 and 1:80 respectively. The diagnosis of Hashimoto thyroiditis was made. Although he had free T4 level in the lower limit of normal, treatment with thyroxine was started because of decrease in activity level. His condition improved after drug treatment.

Group 4 consisted of 9 males and 4 females. There were 3 males and 1 female having compensated PH. Basal TSH ranged from 4.21 to 4.88 mIU/L (Table 1). No patients in this age group received drug treatment.

The overall prevalence of compensated PH was 32% (95% CI=22-42%) for patients with DS from 0.2-18.5 years old. The prevalences for males and females were 33% (95% CI=20-43%) and 31% (95% CI=13-48%) respectively. When different age groups were compared, no statistically significant differences in prevalence of compensated PH were found. One female, 4.7 years of age, was found to have thyrotoxicosis, making the prevalence of 1.3% (95%=0.02-7%) in the whole sample of patients with DS.

Discussion

DS is one of the most common chromosomal disorders encountered in paediatric practice. Patients with DS have various medical problems including thyroid dysfunction. The majority of thyroid problem is PH, which may compromise the physical and mental development in patients with DS. Patients with PH usually did not have symptoms and signs that could be distinguished from those of DS. Therefore a screening approach is necessary in order to detect PH.

There were no cases of CH in our sample and presumably the cord blood or neonatal TSH levels were normal, though no actual data were available in case records. However, we found 4 out of 12 infants (all of them were males) had compensated PH. TRH stimulation test was done in 3 of them and all had peak TSH levels >30 mIU/L, confirming PH before one year of age. The test was not performed in one infant because of parental refusal. However, he had constipation, which could be a symptom of hypothyroidism. In a case control study in Italy, 9 infants having greater basal and TRH-stimulated TSH levels, had their global, verbal and performance intelligence quotient scores significantly lower than normal controls at 6 years of age.[10] Recently, Daliva et al, based on a retrospective study on 14 infants, also advocated treatment in infancy as only one of them could discontinue treatment after 3 years of age.[11]

The proportion of PH of male patients with DS was 33% (95% CI=20-43%) and of female patients was 31% (95% CI=13-48%). There was no statistically significant difference between the two sexes. In addition, our study did not show differences in prevalence in various age groups. Although it was not the objective of our present study, some of the patients had their TSH levels normalised upon serial monitoring. This phenomenon calls for cautious interpretation of a single result of slightly elevated TSH level with normal free T4 level. Thyroxine treatment should not be based on a single finding of a mild biochemical abnormality. Furthermore, the treatment approach to persistent compensated PH is controversial, especially for those with mildly elevated TSH levels. Some would put forward treatment,[12] while others would adopt an observation approach.[13] Besides, evidence shows that iodine deficiency

is present in Hong Kong and this may contributes to the findings of compensated PH in some of our patients.[14]

Since our programme was mainly for screening purpose, thyroid antibodies were not routinely checked. Therefore, data was not available to compare the prevalence of thyroid antibodies between those with PH and those with normal thyroid function. However, a recent report showed that overt thyrotoxicosis or hypothyroidism were always associated with positive thyroid antibodies.[15]

The proportion of thyrotoxicosis in our subject was 1.3% (95% CI=0.02-7%), which was similar to previous study.[5]

In conclusion, thyroid dysfunction is common among local Chinese population with DS. As the majority of these patients are asymptomatic, a screening programme is recommended.[2,5] However, a longitudinal study is necessary in order to detect the time course of compensated PH in children with DS and help in the approach to such biochemical abnormality. Moreover, further studies are needed to clarify whether treatment is indicated for patient with persistent compensated PH with mildly elevated TSH.

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