Thyroid Function in Kuwaiti Subjects with Down's Syndrome

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Key Words

Down's syndrome · Hyperthyroidism · Hypothyroidism ·
Thyroid antibodies · Thyroid function tests

Abstract

Objective: To investigate the thyroid function of individuals with Down's syndrome (DS). **Methods:** Thyroid function and antithyroid antibodies were measured in 58 Kuwaitis with DS who resided at a residential facility or attended rehabilitation centers. **Results:** Twenty-six subjects (45%) were euthyroid and 32 (55%) had thyroid dysfunction. One patient had previously been diagnosed with thyroid failure whereas the other 31 patients had newly discovered disease: 9 patients had primary hypothyroidism (T_4 9.95 ± 1.1 pmol/l and TSH 15.15 ± 11.93 mU/l), 19 subclinical hypothyroidism (TSH 6.47 ± 2.57 mU/l), 1 secondary hypothyroidism, 1 hyperthyroidism, and the remaining 1 subclinical hyperthyroidism. Antithyroid antibodies were found in 52% of the total subjects and in 59% of those with thyroid dysfunction. **Conclusions:** Thyroid dysfunction is common in Kuwaiti subjects with DS and is presumably the consequence of autoimmune thyroid disease. Periodic thyroid function testing is recommended in individuals with DS, which is best done through a national program.

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Introduction

Many cross-sectional studies have documented a high prevalence of thyroid abnormalities in individuals with Down's syndrome (DS) (table 1) [1–18]. Such abnormalities include hypofunction, hyperfunction, positive anti-thyroid antibodies, goiter, abnormal thyroid gland histology, and abnormal thyroid tests, singly or in various combinations. The comparison between these studies is somewhat limited by differences in the selected population and the diagnostic criteria. The most common thyroid abnormality is subclinical hypothyroidism: high serum thyroid-stimulating hormone (TSH) with normal free thyroxine (T_4). The incidence of hypothyroidism in DS is much more than that of hyperthyroidism. Individuals with DS have been shown to have higher mean basal TSH levels and lower mean thyroid hormone concentrations compared with controls [2, 15]. Since the manifestations of hypothyroidism are nonspecific and may be masked by the features of DS, the diagnosis of hypothyroidism in DS largely depends on biochemical testing rather than the clinical features of the disease. These difficulties in ascertaining clinical symptoms – in addition to the generally observed decline in thyroid function with advancing age – highlight the need for periodic thyroid function testing in this population [6, 14]. These tests should include thyroid

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Table 1. Thyroid function studies in DS (in ascending chronological order)

Country	Author	Subjects	Cases	Age years	Control group	Total with thyroid dysfunction, %	Total with thyroid antibodies, %
Australia	Baxter et al. [1]	inpatient	11	44–65	no	63	45
UK	Murdoch et al. [2]	inpatient	82	19–65	yes	40	13.4
Denmark	Korsager et al. [3]	mixed	24	41–60	yes	33	33
USA	Sare et al. [4]	inpatient	121	13–48	no	20	33
UK	Lobo et al. [5]	outpatient	101	5–47	no	16	29
USA	Pueschel and Pezullo [6]	outpatient	151	3–21	yes	27	31
UK	Loudon et al. [7]	outpatient	116	9/12–19 10/12	no	3.4	29
USA	Cutler et al. [8]	outpatient	49	4/12–3	yes	37	8
UK	Kinnell et al. [9]	inpatient	111	22–72	yes	19	29
UK	Mani [10]	inpatient	55	24–67	no	22	16
USA	Friedman et al. [11]	outpatient	138	2–59	no	21.7	39
USA	Zori et al. [12]	mixed	61	5/12–48	no	66	28
Italy	Pozzan et al. [13]	outpatient	108	3/12–38	no	37	12
UK	Dinani and Carpenter [14]	mixed	106	20–67	no	40.5	34
USA	Pueschel et al. [15]	outpatient	181	1–29	yes	16.5	?
Australia	Selikowitz [16]	outpatient	101	2/52–11 4/12	no	13	23
Italy	Rubello et al. [17]	outpatient	344	1–53	yes	34	18
Sweden	Ivarsson et al. [18]	outpatient	70	1–19	yes	25.7	39

antibody testing since they are found in 8–45% of DS subjects (table 1). The general incidence of DS in Kuwait's mixed population is 1.5/1,000 live births, but reaches 3.6/1,000 live births among the Kuwaiti population, which is characterized by a high fertility and consanguinity rate [19]. Most of the large studies of thyroid disorders in DS have originated from the developed Western countries. Except for an earlier case report [20], ours is the first study investigating thyroid function in Kuwaiti subjects with DS.

Subjects and Methods

Subjects

Fifty-eight Kuwaitis with DS who were served by facilities for the disabled were studied. Twenty-five subjects were residents of an institution for the mentally retarded. The remaining 33 lived in the community and attended rehabilitation centers. There were 40 males and 18 females, with a mean age of 24.29 ± 8.82 years (ranging from 11 to 42). Although the age range was large, almost two thirds of the subjects were young adults: 18 in the age-group of 11–19 years, 25 between 20 and 29 years, 12 between 30 and 39, and 3 age 40 or older. Consent was obtained from the next of kin of all subjects, and the study was approved by the Human Subjects Review Committee of the Medical Rehabilitation Center.

The clinical diagnosis of DS was confirmed by Giemsa banding of chromosomes from peripheral lymphocytes. Fifty-seven patients had the trisomy 21 pattern and 1 was mosaic (normal/trisomy 21). Ten subjects had moderate mental retardation, 30 had severe mental retardation, and 18 had profound mental retardation. None of the subjects had a concurrent illness during the time of the study; only 1 patient, who was diagnosed prior to the study with postradioactive iodine hypothyroidism, was receiving thyroxine replacement therapy.

Laboratory Tests

Serum free T_4 was measured by the ELISA/competition kit (Enzyon-Test FT_4 , Boehringer Mannheim, Germany); reference range 11.8–24.6 pmol/l. Serum TSH was measured by the ELISA/one-step sandwich kit (Enzyon-Test TSH, Boehringer Mannheim); reference range 0.23–3.8 mU/l, with a lower detection limit of 0.05 mU/l. The intra-assay coefficient of variation was 2%, and the interassay coefficient of variation was 2.5% for both tests. Antibodies to thyroglobulin and thyroid peroxidase enzyme (TgAb and TPOAb, respectively) were measured by quantitative enzyme immunoassay, using commercial kits (Varelisa, Elias, Germany). Values ≥ 60 IU/ml for males and ≥ 100 IU/ml for females were considered positive, for both antibodies.

Statistical Analysis

Data were expressed as mean $\pm$ SD. Statistical analyses were done using Student's *t* test and Mann-Whitney test. A *p* value < 0.05 was considered significant.

Table 2. Results of thyroid function tests in 58 Kuwaitis with DS

Hormonal values	Subjects		T ₄ , pmol/l (11.8–24.6)	TSH, mU/l (0.23–3.8)	Positive antibodies		Only TgAb	Only TPOAb	TgAb and TPOAb
	n	%			n	%			
Euthyroid	26	45	15.08 ± 1.42	2.41 ± 0.77	10/25	40	3	3	4
Primary hypothyroidism	10	17	9.95 ± 1.10	15.15 ± 11.93	7	70	1	2	4
Subclinical hypothyroidism	19	33	14.41 ± 1.23	6.47 ± 2.57	10/18	56	2	4	4
Secondary hypothyroidism	1	2	9.74	2.55					
Hyperthyroidism (only increased T ₄)	1	2	25.77	0.55	1	–			1
Subclinical hyperthyroidism	1	2	22.08	0.21	1	–	1		
Total with thyroid dysfunction	32/58	55			29/56	52	7	9	13

Results

Twenty-six patients (45%) had both serum-free T₄ and TSH levels within the normal range (table 2). The mean T₄ for these patients was 15.08 ± 1.42 pmol/l (range 12.40 ± 18.89) and the mean TSH 2.41 ± 0.77 mU/l (range 0.42–3.51). The other 31 patients had abnormal T₄ and/or TSH values. Of these, 9 (16%) subjects had a mean TSH of 15.15 ± 11.93 mU/l (range 4.27–39.30) and a mean T₄ of 9.95 ± 1.1 pmol/l (range 8.47–11.58), indicating primary hypothyroidism. Nineteen (33%) subjects had a mean TSH 6.47 ± 2.57 mU/l (range 3.82–13.73), indicating subclinical hypothyroidism. The remaining 3 subjects with thyroid dysfunction had each an individual pattern of decreased T₄ (9.74 pmol/l), elevated T₄ (25.77 pmol/l), or decreased TSH (0.21 mU/l). The first subject further had TRH stimulation test that was normal and an MRI of the hypothalamus-pituitary region, which showed normally enhanced sella turcica with central stalk. These findings are consistent with secondary hypothyroidism. The third subject who had bilateral exophthalmos also had TRH stimulation test, which showed a flat response, consistent with subclinical hyperthyroidism.

The T₄ values for males and females were 14.64 ± 3.07 and 13.70 ± 2.8 pmol/l, respectively ($p = 0.668$). The TSH values for males and females were 4.60 ± 3.61 and 8.01 ± 10.27 mU/l, respectively ($p = 0.217$). There was no statistically significant difference by gender for T₄ and TSH. The T₄ values for primary hypothyroidism and subclinical hypothyroidism were 9.95 ± 1.0 and 14.41 ± 1.23 pmol/l, respectively ($p = 0.384$), indicating that there was no statistically significant difference between the two. The TSH values for primary and subclinical hypothyroidism were 15.15 ± 11.9 and 6.47 ± 2.57 mU/l, respective-

ly ($p = 0.015$), indicating that there was a statistically significant difference between the two.

For antibody testing, 29 were positive, 27 were negative, and the test was not given to 2 patients (1 with normal thyroid function and the other with hyperthyrotropinemia). For the positive patients, 7 had only TgAb, 9 had only TPOAb, and 13 had both. Nineteen (65%) had thyroid dysfunction: 7 had primary hypothyroidism, 10 subclinical hypothyroidism, 1 elevated T₄ and 1 reduced TSH. Thyroid dysfunction was found in 40% of the institutionalized subjects and 57% of the community-living subjects, similar to their corresponding composition (43 and 57%) of the study group, thereby indicating there was no bias in the selection of the subjects.

Discussion

Our study reveals a high frequency of thyroid dysfunction (55%) and of thyroid autoimmunity (52%) in Kuwaitis with DS, many of whom suffer from either severe or profound mental retardation. These values are higher than those of most other reports, partly due to our liberal diagnostic criteria which included individuals with only mildly elevated TSH. However, when our results are compared to those of other studies using similar diagnostic criteria, the values (55%) fall within the reported range (37–66%) of thyroid dysfunction [12–14]. For thyroid antibodies, our value was also higher than those of previous reports (table 1), most probably due to the sensitivity of the test we used (ELISA), compared to those of others (coated red cell hemagglutination). However, the fact that our sample size was relatively small and that we did not have a control group might have affected our results.

No sex difference was seen in T₄ or TSH values, which is in agreement with most studies. Of two dissenting studies, one found more hypothyroidism in males [6] and the other found more hypothyroidism in females under 20 years of age [4]. The TSH level was significantly higher in the group with primary hypothyroidism compared to the group with subclinical hypothyroidism, but the difference in T₄ levels between the two groups was not statistically significant. Our data confirm previous reports that hypothyroidism is much more common than hyperthyroidism in DS [1–18].

The findings of 55% for thyroid dysfunction and 52% for positive thyroid antibodies in this study indicate that the presence of thyroid antibodies constitutes a marker for thyroid dysfunction in people with DS [1–18]. Moreover, we found that the prevalence of positive antibodies increased with the extent of aberration of thyroid function tests: euthyroid 40%, subclinical hypothyroidism 56%, and primary hypothyroidism 70%. Rubello et al. [17]

found that subclinically hypothyroid subjects with positive antibodies were much more likely to develop overt hypothyroidism on follow-up than those with negative antibody results. The findings of this investigation – 55% aberrations of thyroid function tests with 52% positive antithyroid antibodies in Kuwaiti subjects with DS – indicate inadequate screening for thyroid disease. With periodic testing, individuals with significantly abnormal results can be identified early before clinical symptoms become manifest.

Conclusion

Thyroid dysfunction is common in Kuwaiti subjects with DS. This dysfunction resulting from thyroid autoimmune disease increases as the level of thyroid antibodies increases. We recommend routine thyroid function testing in DS subjects, in particular as they advance in age.

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