

ANTITHYROID ANTIBODIES AND THYROID DYSFUNCTION IN SAUDI CHILDREN WITH DOWN SYNDROME

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Fifty children (ages seven months to nine years) with Down syndrome compared with age and sex matched controls were tested for antithyroid antibodies. Seven (14%) of the Down group were found to be seropositive; six (12%) for antimicrosomal antibodies; three for both antimicrosomal and antithyroglobulin; none was positive for antithyroglobulin alone. All the control group were seronegative and had no clinical evidence of thyroid disease. Three (6%) of the Down group had hypothyroidism, two due to autoimmune thyroiditis and one had thyroid dysgenesis; one of the previous two had insulin dependent diabetes mellitus. One child had Graves disease. Thyroid dysfunction was not previously suspected in the two symptomatic children. In view of our findings, recommendations are made to regularly screen these children for autoantibodies and evidence of thyroid dysfunction. *Ann Saudi Med* 1994;14(4):283-285.

The association of Down syndrome with various thyroid disorders, particularly autoimmune thyroiditis, is well known.¹⁻⁴ Though most of the previous studies were done in adults, recently this problem has also been described in younger age groups.^{2,4-9} The symptoms of thyroid dysfunctions may go unrecognized and can be accepted as part of the underlying mental retardation.³ Racial and regional variation in the prevalence of thyroid antibodies is well recognized.^{10,11}

The purpose of this study was to find the prevalence of thyroid antibodies and thyroid disorders among children with Down syndrome attending two pediatric outpatient departments at Security Forces Hospital and Suleimania Children's Hospital in Riyadh, Saudi Arabia and to draw attention of the local pediatricians to it. To the best of our knowledge, no such information on this subject was published from the Kingdom.

Patients and Methods

Fifty children with Down syndrome and an age/sex matched control group attending pediatric clinics at Suleimania Children's Hospital and Security Forces Hospital were randomly selected for our study after obtaining consent from the parents. The clinical diagnosis of Down syndrome was previously confirmed in all the

patients. A total of 49 patients had trisomy pattern and one had translocation.

History pointing to thyroid dysfunction as well as relevant family history was obtained from parents. All children were then clinically examined for evidence of thyroid disorder. Venous blood was then obtained from both groups to be tested for thyroid antibodies. Blood from patients with Down syndrome was also tested for thyroxine and thyrotropin (TSH). No thyroid function tests were done on the control group unless indicated.

Antibodies to thyroglobulin and thyroid microsomal antigens were assayed locally by a passive hemagglutination method using commercial kits (Thymune T and Thymune M hemagglutination kit, Wellcome Diagnostics, Darford, United Kingdom). A titer of 1:100 or greater was considered positive. Thyroxine and TSH were measured by radioimmunoassay using Amersham kits (Amersham International, Emrsham, UK). Thyroid stimulating immunoglobulin (TSI) tests were performed abroad by London Central Laboratories.

Results

Of children with Down syndrome, there were 20 males and 30 females ranging in age from seven months to nine years with a mean of 16.8 months. There were 46 Saudis and four non-Saudis but they were all of Arab origin. Seven (14%) were found to be seropositive, six (12%) for antimicrosomal antibodies, three for both antimicrosomal and antithyroglobulin antibodies, but none had antithyroglobulin antibodies alone. One child with Graves disease had TSI. The clinical details of those who were seropositive are shown in Table 1. Patients 1 to 4 were clinically euthyroid and thyroxine and TSH levels were

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TABLE 1. Details of children with Down syndrome and positive thyroid antibodies.

Patient	Age (months)	Sex	Thyroid Antibodies			Comments
			AT	AM	TSI	
1	4	F	-	+	-	Euthyroid
2	8	F	-	+	-	Euthyroid
3	12	F	+	+	-	Euthyroid
4	3	M	-	+	-	Euthyroid
5	36	M	+	+	-	Goiter, hypothyroidism and IDDM
6	84	M	+	+	-	Goiter with hypothyroidism
7	96	F	-	-	+	Hyperthyroidism (Graves disease)

AT=antithyroglobulin; AM=antimicrosomal; TSI=thyroid stimulating immunoglobulin; IDDM=insulin-dependent diabetes mellitus.

within normal limits. Patient 5 was a known diabetic diagnosed at age 14 months; on examination at age 36 months, he was found to have goiter with low thyroxine of 20 nmol/L (69 to 141 nmol/L) and high TSH of 270 mU/L (0.3 to 3.8 mU/L), yet clinical hypothyroidism was not suspected previously. There was no family history of autoimmune endocrinopathy. In patient 6, symptoms including slower activity were observed by parents two years prior to diagnosis; yet physicians elsewhere attributed them to his primary illness until two weeks before diagnosis, when he was brought to us because they became concerned about his excessive facial puffiness and wanted to exclude a renal problem. He was treated and showed obvious improvement. Symptoms in patient 7 began one year prior to presentation. These included hyperactivity, reduced attention span and poor school performance, which were again initially attributed to her Down syndrome, as the child was attending school for the mentally handicapped. The child was only brought for medical consultation when she started to have frequent bouts of diarrhea, marked weight loss, aches and pains in the lower limbs and unusually prominent eyes. Diagnosis of hyperthyroidism (Graves disease) was confirmed and the child is currently controlled medically. In addition to those with positive antibodies, one seven-month-old child who was referred to the cardiology clinic with ventricular septal defect (VSD) was found to have congenital hypothyroidism and on scanning, was found to have thyroid dysgenesis. This child was born outside Riyadh in a hospital where screening was not available. None of the control group had clinical evidence of thyroid disease and they were all seronegative. No thyroid function tests were done on them.

Discussion

The thyroid dysfunction in individuals with Down syndrome of all ages is a common heterogenous disorder that cannot be solely explained on the basis of

autoimmunity.^{8,9} Congenital hypothyroidism has been reported in children with Down syndrome. In a report from New York, New York, USA,¹² 11 of 1210 infants tested at birth were found to have hypothyroidism. A figure as high as 6% was quoted from another hospital-based study.³ These are higher than the figure of 1:4-5000 quoted from the Western and National Newborn Screening Program in Riyadh.^{13,14} However, this is a small number which needs further verification.

In a recent publication, only 48% of patients over 10 years and 20% of those under 10 years with Down syndrome and thyroid dysfunction were found to have positive antibodies and the rest were seronegative.⁸ Many of these seronegative patients were found to have high TSH with normal free thyroxine level and normal pituitary response to TRH test. Possible explanations given to this phenomenon included: autoimmune thyroiditis with antibodies not detectable with currently available methods, a central disorder in appropriate release of TSH, a less active TSH or a metabolic error.^{8,9} In the series on newborns published from New York, New York, USA,¹² eight infants out of 11 with neonatal hypothyroidism were seronegative and the thyroid gland was demonstrated on scanning and thus the hypothyroidism was attributed to possible dysmorphogenesis.¹² However, higher incidence of thyroid dysgenesis was previously reported in children with Down syndrome^{3,12} and we had one case. Thyroid dysgenesis could also be associated with other congenital anomalies in these cases.^{2,15,16} One of our patients had congenital heart disease with thyroid dysgenesis.

The association between autoimmune thyroid dysfunction and Down syndrome is widely recognized and the incidence varies from 2% to 63%.³ The incidence tends to increase with age. Loudon et al.⁴ reported the presence of thyroid antibodies among 29% of children ages nine months to 20 years and 20% of those under 10 years were seropositive. Lobo et al.⁶ found a 30% incidence and Sare et al.⁷ found antimicrosomal antibodies in 30% and thyroglobulin antibodies in 22% of children between 13 and 20 years. Cutler et al.² demonstrated antibodies in two out of 49 children below two years. Our figure of 12% among all the group is higher than the latter and lower than the previous group. Five of our six cases were below three years. Our lower incidence in comparison to Lobo et al.⁶ and Sare et al.⁷ could be explained by the younger age. Our comparatively higher figure than Cutler et al.² could be due to racial differences. However, a large series might be needed to support our findings. In a previous series we have shown that Arab diabetic children have higher antithyroid antibodies than African Americans.¹⁰

Abbassi and Coleman¹⁷ noted acquired hypothyroidism in 16 of 208 (7.5%) children with Down syndrome ages zero to 16, seven of whom were below four years. Two (4%) of our study group had autoimmune hypothyroidism.

This is lower than the group as reported by Abbassi and Coleman but comparable or slightly higher than the figure of 2% reported by Cutler et al.² among young children.

The prevalence of unrecognized hyperthyroidism among adults with Down syndrome was reported as 1.4%. In children, one study⁴ found one child out of 116 to have hyperthyroidism and in another,² one out of 49 was found to be so. However, it was not mentioned whether all these children had Graves disease and no testing was done for TSI as was done by our group. In two recent publications, two out of 66 and two out of 33 patients with Down syndrome and thyroid dysfunction were found to have Graves disease.^{8,9} It is of interest to note that Hollingworth et al.,¹⁸ studying 60 older children and adults with Down syndrome, found them to have exophthalmos without goiter or thyroid dysfunction. Though we treated our patients with drugs, recent publications, particularly from North America, have shown that physicians are prescribing radioactive iodine more liberally to treat thyrotoxicosis in older children than had been previously practiced.¹⁹ Perhaps children with Down syndrome would be more appropriate candidates for this form of therapy if medical treatment fails.

Down syndrome has been linked with autoimmune disorders including alopecia areata, vitiligo, diabetes mellitus, adrenal dysfunction, pernicious anemia, chronic active hepatitis, gluten enteropathy and hemolytic anemia.²⁰⁻²³ We do not have the facilities to test for other organ-specific antibodies. Our case of diabetes mellitus tallies this observation.

Untreated thyroid disease can have a significant impact on the behavior and functioning of persons with Down syndrome. The symptoms of thyroid dysfunction may go unrecognized in these cases as they are often attributed to their primary illness, as happened to two of our cases. In a recent study,³ unrecognized thyroid dysfunction was demonstrated in 20.3% of persons with Down syndrome living in a community. Therefore, it has been recommended that all patients with Down syndrome should undergo an initial clinical and laboratory screening for the presence of thyroid dysfunction including antibodies and should thereafter be regularly followed up at six month to one year intervals. Those with positive antibodies, clinical or biochemical evidence of the disease, should then be further evaluated and treated.^{2-4,8,9} On the basis of our findings, we strongly support this recommendation.

In conclusion, we have demonstrated a higher than normal prevalence of thyroid antibodies and variable spectrum of thyroid dysfunctions in Saudi children with Down syndrome as experienced elsewhere. Until further studies with larger samples are conducted in the Kingdom,

we recommend that all children with Down syndrome in the Kingdom of Saudi Arabia be screened regularly for thyroid antibodies as well as for evidence of thyroid dysfunction and treated accordingly.

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