Thyroid dysfunction in Down's syndrome

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SUMMARY One hundred and sixteen children with Down's syndrome, living in the community, were examined for clinical or laboratory evidence of thyroid dysfunction. Three were hypothyroid and one was hyperthyroid. Twenty eight (29%) had thyroid autoantibodies. Autoimmune conditions were present in first or second degree relatives of 35 (30%) of the children, and in 17 (15%) this was a thyroid disorder. The families of normal control children also showed a 30% incidence of overt autoimmune conditions, and 19 (16%) families showed overt thyroid disease.

Individual case reports of hypothyroidism and hyperthyroidism occurring in children with Down's syndrome have been described for many years, but only in the last decade has an unexpectedly high incidence been recognised. An increased prevalence of thyroid antibodies in the serum of both adults and children has been noted,¹ sometimes accompanied by hypothyroidism in the adult population.²⁻³ More recently, where the group of patients screened has included children, chronic lymphocytic thyroiditis has been shown regularly in the younger age groups also.⁴⁻⁶

Down's syndrome has been linked with other autoimmune disorders. Alopecia areata and vitiligo are seen more often than normal⁷⁻⁸ and diabetes mellitus, adrenal dysfunction, pernicious anaemia with chronic active hepatitis,⁹ and gluten enteropathy with haemolytic anaemia¹⁰ are described less commonly. This would suggest an aetiological association, which is either peculiar to Down's syndrome or genetically determined.

We studied children with Down's syndrome, living at home in our area, for evidence of thyroid abnormality to determine the incidence of thyroid autoantibodies in the children and the occurrence of overt autoimmune disorders in their relatives.

Patients and methods

Parents of children with Down's syndrome were contacted through the community child health services. Altogether, 116 families agreed to take part in the study. There were 67 boys and 49 girls. Ages ranged from 9 months to 19 years 10 months, with a mean age of 11.3 years for boys and 12.8 for girls.

The children, accompanied by one or both parents, attended the outpatient department. Details were asked of the child's birth, karyotype, development, past illnesses, symptoms of thyroid dysfunction, and family history. The height and weight were measured and an examination made for goitre and signs of thyroid disease. Blood was taken for estimation of triiodothyronine, thyroxine, and thyroid stimulating hormone concentrations by radioimmunoassay. Antibody titres to thyroglobulin and thyroid microsomal antibody were measured using Wellcome Laboratory's Thymune T and Thymune M Haemagglutination Kits.

When taking the family history, we enquired closely about thyrotoxicosis, myxoedema, Hashimoto's thyroiditis, goitre, insulin dependent diabetes mellitus, pernicious anaemia, rheumatoid arthritis, and Addison's disease. Some error in reporting was likely to occur, but specific details were taken, and any that seemed doubtful were excluded. The same history was taken from the parents of 116 control children who were attending the outpatient department with unrelated medical and surgical conditions. They did not have a relative with Down's syndrome. This control group could be criticised as not being made up of strictly normal children.

Results

Thyroid function tests. Three children had low serum thyroxine and raised thyroid stimulating hormone concentrations, suggesting primary hypothyroidism, and one child was thyrotoxic (Table 1). The two boys, whose thyroxine concentrations were in the low normal range, showed an exaggerated response of thyroid stimulating hormone to

Table 1 Results of tests of children with Down's syndrome with abnormal thyroid function

Sex	Age (years)	Bone age (years)	Thyroxine (nmol/l)	Thyroid stimulating hormone (mμl/l)	Thyrotrophin releasing hormone test	Antibodies	
						T	M
M	10	10.2	58	Hypothyroid 24.7	Positive		1600
M	17	18+	54	31.6	Positive	20	100
F	17	10.7	18	> 60			6400
F	16		> 250	Hyperthyroid <1.6			

Normal ranges: thyroxine 55–144 nmol/l; thyroid stimulating hormone 0–8.0 mμl/l.

Table 2 Incidence of antibodies in children with family history of autoimmune disease

Disorder	Positive family history in children with Down's syndrome (No (%))	Children with thyroid antibody (%)	Positive family history in control children (No (%))
Thyroid	17 (15)	42	19 (16)
Pernicious anaemia	8 (7)	71	3 (3)
Diabetes mellitus	6 (5)	50	10 (9)
Rheumatoid arthritis	12 (10)	55	17 (15)

thyrotrophin releasing hormone. There was no significant difference in mean thyroxine concentrations between the sexes (90 μmol/l in boys and 93 μmol/l in girls).

Thyroid antibodies. Titres were available for 95 children. Thyroglobulin antibody was found in eight, the titre range being 10–160. Microsomal antibody was positive in 26, with titres of 100–102 400. At least one antibody was positive in 28 (29%) of the group, and occurred in 32% of boys and 24% of girls. In normal children of this age, one would expect to find thyroid antibodies in 0–7%.^{1 11} All three hypothyroid patients had antibodies. Their titres were moderate.

Family history. A first or second degree relative of 35 (30%) of the children had one of the autoimmune conditions mentioned above. Not unexpectedly, the incidence of thyroid antibodies was higher in these children (Table 2). In eleven families two different conditions existed. Although thyroid disease was reported in 17 families, in only five cases did the child tested have antibodies.

In the control group the percentage incidence of a family history of autoimmune disease was remarkably similar to the group with Down's syndrome.

Other autoimmune conditions

Alopecia areata was diagnosed in four children. It had become universal in three boys, all of whom had thyroid antibodies, and two of whom were

hypothyroid. The association is fairly common,^{7 8} and the extent of hair loss has been reported to be more extensive than usual.¹² One girl developed diabetes mellitus during the course of the study. She had a low thyroglobulin antibody titre.

Discussion

Children who have Down's syndrome, like adults, commonly have thyroid antibodies in the serum and are at risk of developing overt thyroid dysfunction, especially hypothyroidism. The association of antibodies and thyroid disease strongly suggests an autoimmune pathogenesis.

Although none of the children in this study had their thyroid states checked earlier in life, the timing of symptoms and clinical findings in the three boys who were hypothyroid point to onset of chronic atrophic thyroiditis in later childhood. Normal bone age in two cases, and a seven years' delay in bone age in the girl, confirm this. None had goitre.

The presence of autoantibodies in 28 (29%) of the population is similar to other childhood studies. Lobo *et al* found a 30% incidence,⁵ and Sare *et al* found antimitochondrial antibody in 30% and thyroglobulin antibody in 22% of children aged between 13 and 20 years.⁴ Sare noted, however, that girls were positive twice as often as boys, whereas boys were more often positive than girls in our study. Autoantibodies can be produced by very young children. They have been reported in a 2 year old and two 3 year old euthyroid boys and in a 2 year old hypothyroid girl. Of this population, 20% aged

under 10 were positive, and the youngest was 5 years old. He had a microsomal antibody titre of 25 600.

The prevalence of hypothyroidism in children with Down's syndrome is variable. Lobo *et al* found that 4% of children aged under 21 were affected,⁵ Sare *et al* that 17% aged under 20 were affected,⁴ and Coleman *et al* noted that 8% aged under 18 were affected.⁶ The picture is made more uncertain by the discovery by Fort *et al* of primary non-goitrous hypothyroidism in 11 of 121 infants with Down's syndrome tested during the New York state screening programme. It persisted in eight. Those who were tested had no thyroid antibodies and a normal thyroid gland on isotope scanning.¹³

The occurrence of familial aggregation of autoimmune disorders is well known, and the relatives in such families often form autoantibodies. We were not surprised when 50% of children with Down's syndrome from families harbouring an autoimmune disorder had antibodies. Even by excluding the children from such families, 18% were still positive. Fialkow¹⁴ and Vanhaelst¹⁵ have each reported a high rate of thyroid disease within families of children with Down's syndrome, but this study does not agree. Thyroid antibodies were present in 27% and 29%, respectively, of their mothers, and siblings are often positive. Perhaps this is reflected in the children.

The many thymus dependent immunological abnormalities described in Down's syndrome¹⁶⁻¹⁸ may help to explain the occurrence at a very young age of autoimmune thyroiditis, which is thought to be due to a genetically determined, organ specific defect in suppressor T lymphocytes.¹⁹ Reasons for the condition's heterogeneity were recently clarified by the discovery of thyroid stimulating hormone receptor blocking and enhancing immunoglobulins, which affect selectively hormone synthesis and thyroid gland growth.²⁰

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