

Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity

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Abstract

Background—The prevalence of thyroid disease is increased in Down's syndrome. Most available data come from cross sectional studies.

Aims—To study longitudinally thyroid function in patients with Down's syndrome in Uppsala county (85 patients) up to the age of 25 years.

Methods—Observational study based on yearly follow up in a children's clinic. Thyroid function tests were performed at each visit to the clinic.

Results—Hypothyroidism was found in 30 and hyperthyroidism was found in two of the 85 patients. No sex difference was seen. Half of the patients with hypothyroidism acquired the condition before the age of 8 years, but only one of them displayed thyroid autoantibodies at diagnosis. Most patients who developed hypothyroidism after this age had thyroid autoantibodies. In the prepubertal patients with hypothyroidism, growth velocity was lower during the year before the start of thyroxine treatment than during the year after treatment began; it was also lower than that of sex and age matched euthyroidic children with Down's syndrome.

Conclusion—Thyroid dysfunction in patients with Down's syndrome is common in childhood. Consequently, annual screening is important. Autoimmune thyroid disease is uncommon in young children with Down's syndrome but is common after 8 years of age.

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Keywords: Down's syndrome; hyperthyroidism; hypothyroidism; thyroid function

Down's syndrome is one of the most common chromosomal disorders (one in 800 births) and the most common cause of mental retardation. It is well known that patients with Down's syndrome have an increased prevalence of autoimmune disorders affecting both endocrine and non-endocrine organs.¹ The most common autoimmune disease in Down's syndrome is related to the thyroid gland. Thyroid autoantibodies are found in 13-34% of patients with Down's syndrome.²⁻¹⁰ Thus, both hypothyroidism and hyperthyroidism are more common in patients with Down's syndrome than in the general population.¹¹ The reported prevalence of hypothyroidism in adults with Down's syndrome has varied between 3% and 54%.^{3-7 10 12 13} Studies by our group and other authors have also shown an increased risk of

thyroid disease among children with Down's syndrome.^{2 4 8 10 11 14}

The aim of our investigation was to study thyroid function longitudinally in all children and young individuals with Down's syndrome living in the county of Uppsala in relation to age, sex, growth velocity, and presence of thyroid autoantibodies. The results from 85 children with Down's syndrome followed up annually for up to 15 years are reported.

Materials and methods

PATIENTS

All children, adolescents, and young adults with Down's syndrome in the county of Uppsala (n = 93) who were being followed up at least once yearly at the Uppsala University Children's Hospital within the frame of a medical care and support programme for individuals with Down's syndrome¹⁵ were included initially in the study. There were 47 boys and 46 girls. The patients were between 1 and 25 years old. Eight of these 93 patients were excluded from the study, six because of other medications (four boys and two girls) and two because of heart failure (one boy and one girl). Thus, the study comprised 85 patients (42 boys and 43 girls). Of the 85 individuals in our longitudinal study, 25 had been included in an earlier cross sectional investigation on thyroid function in Down's syndrome in Uppsala and Malmö.¹⁰

Hypothyroidism was diagnosed on the basis of a combination of a raised serum concentration of thyroid stimulating hormone (TSH) and either a low serum concentration of free thyroxine (T₄), or a marginally low concentration of free T₄ combined with the presence of symptoms associated with hypothyroidism (constipation, dry skin, weight gain, and decreased growth velocity relative to the Down's syndrome growth chart).¹⁶

For the assessment of growth velocity in relation to thyroid function, eight Down's syndrome children who developed hypothyroidism at the ages of 2-11 years were compared with eight age and sex matched euthyroidic children with Down's syndrome. Growth rates (cm/year) were calculated during the year before and the year after the start of thyroxine treatment in the children with hypothyroidism and compared with the corresponding growth rates of the euthyroidic children with Down's syndrome.

LABORATORY TECHNIQUES

TSH, total T₄, and free T₄ were measured by routine in-house methods. Thyroglobulin autoantibodies (Tg-ab) and thyroid peroxidase

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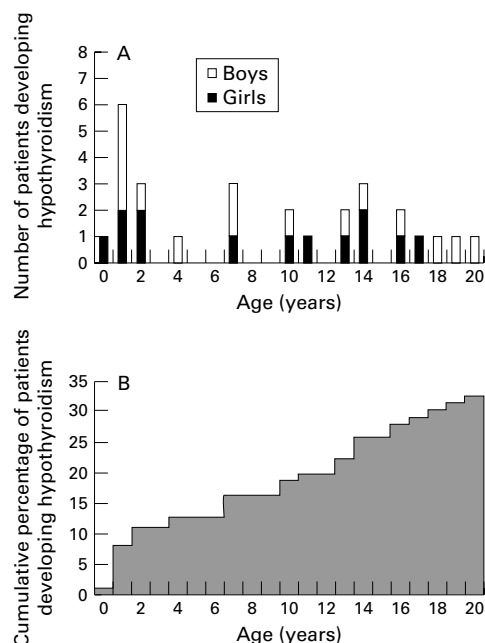


Figure 1 (A) Relation to sex and age at time of development of hypothyroidism. (B) Cumulative percentage in relation to age in the 28 children and young individuals with Down's syndrome who developed hypothyroidism.

autoantibodies (TPO-ab) were both measured in the same laboratory with a sensitive solid phase immunosorbent radioassay described previously.¹⁷ In short, 100 μ l of human serum was mixed with 400 μ l ¹²⁵I labelled Tg or TPO and incubated overnight at 4°C. An aliquot of 50 μ l of this mixture was then mixed with 250 μ l of a suspension of antihuman IgG covalently coupled to Sepharose, and incubated for another two hours at room temperature, after which 1 μ l 0.075 M barbital buffer (pH 8.6) containing 0.2% bovine serum albumin was added. The suspension was centrifuged (2400 \times g) for 15 minutes at 4°C and the supernatant was decanted.

The washing procedure was repeated once. The radioactivity was measured in the precipitate. All samples were assayed in duplicate at a final dilution of 1/5–1/5 000 000 until binding

reached the detection limit that had been established with sera that showed low and unchanged binding at successive dilutions. The level of non-specific binding was controlled in each run. The value obtained at one dilution step before this level was taken as the titre. Positive sera dilution curves (plotted with the percentage of bound activity of the labelled antigen on the Y axis and the dilution on the X axis) conformed with dilution curves of standards from the Medical Research Council (MRC Standard A65/93 for Tg and 66/387 for TPO). If the antibodies were present at a titre of 1/5 or more, the sample was considered to be positive.

STATISTICAL METHODS

The paired *t* test was used for analysis of the data.

Results

None of the patients studied had congenital hypothyroidism. During the follow up period thyroid dysfunction developed in 30 of the 85 children (hypothyroidism in 28 (15 boys and 13 girls) and hyperthyroidism (thyrotoxicosis, Graves disease) in two (both girls)). No sex difference was seen among the patients with hypothyroidism (fig 1). As seen in fig 1, half of the subjects with hypothyroidism (14 of 28) acquired the condition before the age of 8 years. The mean serum concentration of TSH in all age groups was slightly raised or in the upper normal range (0–1 year, 4.8 mU/l; 2–6 years, 3.5 mU/l; 7–10 years, 4.2 mU/l; 11–15 years, 3.3 mU/l; > 15 years 4.8 mU/l; normal range from infancy to adulthood, 0.3–4 mU/l).

The occurrence of serum thyroid autoantibodies at the time of clinical diagnosis is shown in fig 2. Only one analysis was performed for each patient. Of the children tested (11 of 14) for thyroid autoimmunity, only one child with hypothyroidism displayed a detectable serum TPO-ab concentration and none were positive for Tg-ab before the age of 8 years. Of the euthyroid children with Down's syndrome, two displayed raised TPO-ab concentrations

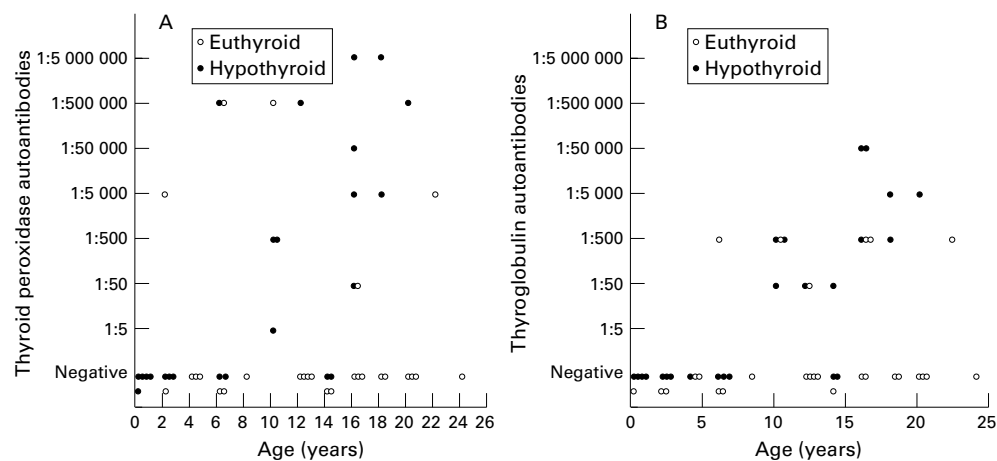


Figure 2 The presence of (A) thyroid peroxidase autoantibodies (TPO-ab) and (B) thyroglobulin autoantibodies (Tg-ab) among 53 individuals with Down's syndrome in relation to age and thyroid function (hypothyroidic or euthyroidic). Only one analysis was performed for each subject. The concentrations of Tg-ab and TPO-ab in the 24 children with hypothyroidism correspond to the time of the clinical diagnosis.

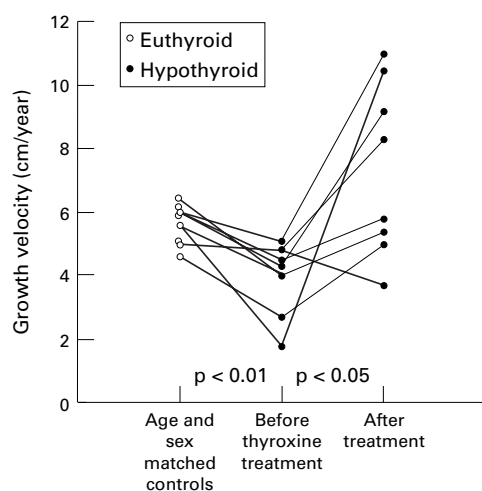


Figure 3 Growth velocity (cm/year) in eight children with Down's syndrome and hypothyroidism during the year before the start of thyroxine treatment compared with the year after treatment began and with eight age and sex matched euthyroid children with Down's syndrome. All the children were prepubertal (age range, 2–11 years).

and one a raised Tg-ab concentration. Half (14 of 28) of the patients with hypothyroidism acquired the disease after the age of 8 years and 11 of the 13 who were tested had raised concentrations of one or both autoantibodies. Of the euthyroid children with Down's syndrome in the latter age group, three had raised TPO-ab concentrations and five had raised Tg-ab concentrations.

In the eight children with Down's syndrome who developed hypothyroidism during the childhood growth period¹⁸ (between the ages of 2 and 11 years), the mean (SEM) growth velocity was significantly lower during the year before the start of thyroxine treatment (4.0 (0.4) cm) compared with the year after treatment began (7.4 (1.0) cm; $p < 0.05$) as well as compared with that of sex and age matched euthyroid controls with Down's syndrome (5.6 (0.2) cm; $p < 0.01$) (fig 3). Growth velocity increased in seven of the eight treated patients. One boy did not increase his growth rate, even though the serum thyroid hormone concentrations (TSH 46.0 mU/l, free T4 5.6 nmol/l before treatment) were normalised by the treatment.

Discussion

Thyroid dysfunction, particularly hypothyroidism, is very common in Down's syndrome, although the available data come from cross sectional studies. The present investigation is a longitudinal study of thyroid function in children and young individuals with Down's syndrome. Our finding of hypothyroidism in a third of this group of patients with Down's syndrome might be compared with the prevalence rates of 3–54% reported earlier among patients with Down's syndrome of all ages.^{3–7 10 12 13} The variation in prevalence in these earlier studies might be related to the age variation among the studied subjects and/or to differences in diagnostic criteria. Because many of the children are young, the incidence of hypothyroidism in our group will probably

increase in the follow up period. Signs and symptoms of hypothyroidism can be difficult to discriminate from those found in the natural course of Down's syndrome itself. This has been reported to be true for dementia associated with hypothyroidism in Down's syndrome.¹⁹

Congenital hypothyroidism has been reported to be about 30 times more common in newborns with Down's syndrome than in healthy newborns.^{2 14} There were no cases of congenital hypothyroidism among our patients, although the results indicate the occurrence of thyroid hypoplasia in some of them. This finding suggests that there could be genes on chromosome 21 involved in thyroid development. However, recently we excluded linkage to any region of the long arm of chromosome 21 in the aetiology of familial cases of presumably autosomal recessive congenital hypothyroidism (Edman Ahlbom B *et al*, unpublished data).

Half of the children in our study developed hypothyroidism at a young age and, in this group, thyroid autoimmunity was found in only one case. The impaired thyroid function in these children might be caused by an insufficient thyroid size in relation to the increasing metabolic demands accompanying an increased body size. Because we found a gradual increase in the concentrations of thyroid autoantibodies from the age of 8 years, it would seem that thyroid autoimmunity could have a clinical impact in Down's syndrome from this age.

We found no sex difference with regard to the incidence of hypothyroidism. This is in contrast to previous observations among both children and adults with hypothyroidism, in whom a female preponderance was found.²⁰

A short stature is one of the cardinal signs in Down's syndrome,¹⁴ and it has been shown to be the result of a selective deficiency of insulin-like growth factor 1.²¹ It can be prevented by growth hormone treatment, at least in young children with Down's syndrome.²² Hypothyroidism might be another reason for growth retardation in Down's syndrome. We found that during the year before the start of thyroxine treatment, the children with hypothyroidism had a lower growth rate than the corresponding euthyroid children with Down's syndrome. Their growth improved during the first year of treatment.

According to our experience, thyroxine replacement treatment should be encouraged, even in cases of marginal hypothyroidism, because such treatment will prevent the development of a more severe hypothyroidic state. Thyroxine replacement is simple to carry out in practice and we have not encountered any adverse effects in this group of patients.

Among the patients with Down's syndrome and thyroid disease, two had thyrotoxicosis associated with high concentrations of TSH receptor stimulating antibodies. This agrees with earlier reports that Down's syndrome children also run higher risks of thyroid hyperfunction compared with healthy subjects.⁵

In summary, hypothyroidism develops in one third of patients with Down's syndrome before the age of 25 years. Autoimmune thyroid disease is uncommon in preschool children with Down's syndrome, but occurs commonly after the age of 8 years. Because symptoms of hypothyroidism might be mistaken for symptoms related to the natural course of Down's syndrome, it is important to screen annually for thyroid function.

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