Original

Hyperthyroidism in Down Syndrome

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Abstract

Thyroid conditions, particularly hypothyroidism, are common in people with Down syndrome (DS). Hyperthyroidism is also found at a higher-than-average rate in patients with DS, although only isolated case reports and short series had been published up until now. We recently published the longest series so far examining the relationship between hyperthyroidism and DS. A systematic review of the 1,856 patients seen at Fundació Catalana Síndrome de Down (FCSD) from 1991 to 2006 was undertaken, and 12 cases of hyperthyroidism were diagnosed. The etiological cause was found to be Graves disease in all cases. After initial treatment with antithyroid drugs, all patients required permanent treatment with radioactive iodine I-131. Annual biochemical screening for early diagnosis is less effective than it is for hypothyroidism. Hyperthyroidism may influence growth and development in children with DS; treatment can reverse its impact.

Keywords: Hyperthyroidism. Down syndrome. Graves disease. Thyroid gland. Growth.

Introduction

Patients with Down syndrome (DS) have more medical conditions than the general population; thyroid disorders are among these conditions (1, 2). Surveys of thyroid disorders among the population with DS give varying prevalence rates because of different sample sizes, selected population and diagnostic criteria, but the actual rate is estimated to be higher than 15% (3, 4, 5). Hypothyroidism, particularly in the form of subclinical hypofunction or, more rarely, as a clinical manifestation, is the most frequent thyroid disorder and endocrine condition at large associated with DS (6, 7). Its prevalence among the population with DS is estimated at 30 to 40% (8, 9).

Hyperthyroidism is also more prevalent among people with DS than in the general population, though the gap is smaller (10, 11). The available literature is largely circumscribed to isolated case reports (6, 11). We recently managed to analyze and describe the most extensive series of cases published so far on the relationship between hyperthyroidism and DS (12). The aim of our study was to investigate the features of hyperthyroidism in patients receiving care at the Fundació Catalana Síndrome de Down (FCSD)'s Centre Mèdic Down, a medical center specializing in DS. Its history, the number of patients it caters to, and its multidisciplinary team of professionals, make the FCSD an important source of knowledge generation for DS-linked conditions in order to improve quality of life for individuals with DS.

The aim of the present article is to address our findings in greater depth and analyze the impact of hyperthyroidism on growth in terms of weight and height.

Materials and methods

A systematic review was made of the 1,832 clinical histories recorded at the FCSD from January of 1991 to February of 2006. All patients with hyperthyroidism

were identified and, once the diagnosis had been established, the following variables were recorded: age, anthropometric measurements, clinical features (palpitations, insomnia, heat intolerance, profuse sweating, nervousness, increased bowel movements, distal tremor, weight loss), physical examination (including thyroid, eye gland, and heart rate), and laboratory tests (TSH, free T4, total T3, antiperoxidase antibodies - ánti-TPO - , antithyroglobuline - anti-TG - and thyroid stimulating immunoglobin - TSI - an antibody against the TSH receptor). Family histories of thyroid disease were recorded, and the presence of other autoimmune disorders was tested for. Technetium 99 scintigraphy was performed for all patients; thyroid ultrasound, on the other hand, was only performed in cases selected by the endocrinologist. Patients were followed on a bi-monthly basis and always seen by the same endocrinologist (A.G-A.) during the study period.

Results

Of 1,832 patients with SD seen at the FCSD from January 1991 to February 2006, 12 (5 male and 7 female) were diagnosed as having hyperthyroidism. The prevalence among this particular population with DS was thus 6.55 cases per 1,000 patients, with an estimated incidence of 43.67/100,000 per year. Mean age was 16.8 years (range: 10.9 to 28.9); mean weight, 42.5 kg (range: 24.5-68.8 kg) whereas mean height was 142.6 cm (range: 123.4-153 cm). Six months after the onset of treatment, mean weight increase was 11.4 kg with mean height growth at 5.3 cm. Table I sums up the clinical features of the 12 patients with hyperthyroidism and SD. All patients were diagnosed clinically, rather than during the yearly screening for thyroid function included as part of the health care program for patients with DS.

As for symptoms of hyperthyroidism at the time of diagnosis, 11 patients had heat intolerance and excessive sweating; 10 were increasingly irritable; 10 had lost weight in preceding months (average, 4.7 kg weight loss, range 1-10 kg); 9 had palpitations, 7 insomnia, 7 distal tremor, 4 increased bowel movements, and 3 complained of eye irritation (Table II). Physical examination findings were as follows: heart rate, 93.9 bpm (range 80-132); diffuse goiter was found in all patients upon inspection of the thyroid gland (WHO grade 2 in 11 cases, grade 3 in 1 case). Two patients had exophthalmos, and none had pretibial myxedema.

Table III displays the growth status of all 12 cases at the time of diagnosis and 6 months into treatment for hypothyroidism, with a reference for comparison to growth charts for the general population and for people with DS.

As for laboratory testing, all patients had undetectable levels of TSH, with elevated free thyroxine at an average 63.7 pmol/L (range 24.5-158.6 pmol/L) (normal range 9-19.4 pmol/L); mean total T3 11.2 nmol/L (range 2.8-22.8 nmol/L) (normal range

Table I.
Clinical features of the 12 patients with DS and hyperthyroidism

	Gender	Age at diagnosis (years)	Etiology	T4L at diagnosis (pmol/L*)	TSI	Antithyroid antibodies**	Comorbidities	Goiter	Ophthalmo-pathy	Family history	Scintigraphy
1	Female	10.9	Graves	32.1	+	+	Myasthenia Congenital heart disease	Grade 2	-	+	-
2	Female	11	Graves	43.2	+	+	Vitiligo Congenital heart disease	Grade 2	-	+	Diffuse uptake
3	Female	11.3	Graves	91.6	+	+	No	Grade 3	-	-	-
4	Female	17.5	Graves	64.5	+	+	No	Grade 2	-	-	Diffuse uptake
5	Female	19	Graves	37.4	+	+	No	Grade 2	-		Diffuse uptake
6	Female	20	Graves	158.6	+	+	No	Grade 2	+	-	Diffuse uptake
7	Female	21.1	Graves	60.6	+	+	No	Grade 2	-	-	Diffuse uptake
8	Male	10.3	Graves	27.5	+	+	Alopecia areata	Grade 2	+	-	-
9	Male	12.2	Graves	44.9	+	+	No	Grade 2	-	-	Diffuse uptake
10	Male	19.5	Graves	103.2	+	+	No	Grade 2	-		Diffuse uptake
11	Male	20.1	Graves	65.8	+	+	No	Grade 2	-	-	Diffuse uptake
12	Male	28.9	Graves	51.2	+	-	No	Grade 2	+	-	-

* Normal range: 9.0-19.4 pmol/L.
** anti-TPO or anti-Tg

1.2-2.5 nmol/L). TSI levels were raised for all patients, with a mean value of 128.1 U/L (range 10-620 U/L) (normal value < 10 U/L). Anti-TPO antibodies were present in 92% of cases (11/12 patients) and anti-TG antibodies in 33.3% (4/12 patients). Hence, almost all patients displayed at least two positive markers of thyroid autoimmunity.

Tc99 scintigraphy objectively showed diffuse increased uptake in all patients, which suggested a diagnosis of Graves-Basedow disease. Ultrasound imaging was only performed on 2 patients and showed diffuse goiter with no nodules.

Carbimazol treatment was initiated for all patients at the time of diagnosis, at a starting dose of 10 mg tid. The daily total dose was subsequently adjusted based on regular test results for thyroid function, until permanent treatment was administered. No patient experienced carbimazol side effects such as rashes, leukopenia or agranulocytosis. Withdrawal of carbimazol was attempted in all cases, but no patient achieved remission for longer than 6 months.

Radioactive iodine was prescribed in cases of recurrence or after 24 months on carbimazol without the possibility of withdrawing this treatment. Parents and guardians were informed of the risks and benefits of this treatment for purposes of informed consent. The patients were informed as well, although they lacked the mental capacity to decide on the matter.

Permanent treatment with I131 was administered after an average 40.3 months of medical treatment (range 10-96 months). Only 2 patients remained on carbimazol due to their family's refusal to allow iodine treatment. All patients developed hypothyroidism following radioiodine therapy and required levothyroxine replacement treatment.

As for comorbidities, 2 patients had a diagnosis of congenital heart disease. A total of 4 patients (33%) had another associated autoimmune condition: celiac disease (2 cases), atopia (1 case), myasthenia gravis (1 case) vitiligo (1 case) and alopecia areata (1 case). There was no association with type 1 diabetes.

Table II.
Frequency of symptoms in the 12 patients with DS and hyperthyroidism

Symptom	Frequency (%)
Heat intolerance	91.6
Excessive sweating	91.6
Irritability	90.9
Weight loss	90.9
Palpitations	75
Insomnia	58.3
Distal tremor	58.3
Increased bowel movements	33.3
Eye irritation	25

Discussion

The majority of studies of thyroid function in DS show a low prevalence of hyperthyroidism, which is generally below 3% (13, 14, 15, 16). Our study is to this date the longest series of cases published for DS (12). Our prevalence rate was 6.5/1,000, with an incidence of 43/100,000 per year, both figures seemingly higher than those for the general population although epidemiological studies of thyrotoxicosis are

Table III.
Weight and height at diagnosis and 6 months after onset of treatment. Comparison to growth tables for DS and for the general population (41)

	At dignosis						6 months after onset of treatment			
Patient	Gender	Age at diagnosis	Height percentile for DS	Height percentile for the general population	Weight percentile for DS	Weight percentile for the general population	Height percentile for DS	Height percentile for the general population	Weight percentile for DS	Weight percentile for the general population
1	Female	10a+9m	P25-50	<P3	<P3	P10	P50	<P3	P25	<P3
2	Female	11a	P50-75	P3	P10	P3	P90	<P3	P50-75	P3
3	Female	11a+3m	P50	P3	P3	<P3	P50	<P3	P25	<P3
4	Female	17a+6m	P75	<P3	>P97	P90	P75	<P3	>P97	>P97
5	Female	19a	P10	<P3	P3-10	<P3	P10	<P3	P25	<P3
6	Female	20a	P75	P3	P90-97	P50-75	P75	P3	P97	P75
7	Female	21a+1m	P25	<P3	<P3	<P3	P50	<P3	<P3	<P3
8	Male	10a+3m	P25-50	P3	P25-50	P25-50	P50-75	<P3	P90	P50
9	Male	12a+2m	P75	P10	P25	P50-75	P75	<P3	<P3	<P3
10	Male	19a+6m	P50	<P3	P50	P3	P50	<P3	P75	<P3
11	Male	20a+1m	P50	<P3	P25-50	<P3	P50	<P3	P75-90	P25-50
12	Male	28a+11m	P50	<P3	P10-25	<P3	P50-75	<P3	P97	P75-90

few and far between. One Danish study gave an incidence among young people of 0.79/100,000 per year with a clear predominance of females (6.7:1) (17). A study of a Japanese population rated the prevalence of Graves disease and other-cause thyrotoxicoses at 0.1% (18). Looking at a population closer to our own, one study of a Spanish population rated the incidence of Graves disease at 24.24/100,000 per year (19). The second longest series of cases with DS published so far, with a total of 181 patients, gave a prevalence rate of 0.5% (20).

DS is often associated with autoimmune disorders, particularly thyroid diseases (10, 21), which are sometimes underdiagnosed (22). Almost 30% of the population with DS has elevated levels of antithyroid antibodies, whose presence has been linked to thyroid dysfunction. One study of 61 patients with DS aged 5 months to 48 years found that 88% of patients with antithyroid antibodies had some kind of altered thyroid function, with subclinical hypothyroidism the most frequent finding (23).

In the literature, Graves disease is the most frequent cause of hyperthyroidism in DS (6, 11, 21, 23, 24, 25). This is clearly borne out in our own study, in which all

Table IV.
Hyperthyroidism and DS. Bibliographic review

Author	Year	Cases	Population screened revalence (%)	Population	Clinical features	Etiology	Associated conditions	Initial treatment	Permanent treatment
Hollingswoth DR	1974	2	60 (3,3)	Both	Goiter	-	-	-	No
Baxter RG	1975	1	11 (9,2)	Adults	-	-	-	Carbimazol	-
Murdoch JC	1977	1	82 (1,2)	Adults	-	-	-	-	-
Fort P	1984	3	121 (2,5)	Children	-	Graves	-	-	-
Pueschel SM	1985	0	151 (0)	Both	-	-	-	-	-
Loudon	1985	1	116 (0,8)	Children	-	-	-	-	-
Cutler A	1986	1	49 (2)	Children	Retarded growth	Graves	-	PTU	No
Zori RT	1990	5	61 (3,2)	Both	-	3 thyroiditiss 2 Graves	Gastric atrophy	- -	- -
Dinani	1990	1	106 (0,9)	Adults	-	-	-	-	-
Pozzan	1990	2	108 (2)	Both	-	Graves	-	-	-
Pueschel SM	1991	1	181 (0,5)	Children	No	-	-	-	-
Colombo ML	1992	1	45 (0)	Both	No	-	Cardiopathy	-	-
Selikowitz M	1993	0	101 (0)	Children	-	-	-	-	-
Tambyah PA	1993	2	-	Adults	-	Graves	-	-	-
Sridhar GR	1997	1	-	Children	-	-	-	-	-
Bhowmick	1997	5	-	Children	-	Graves		PTU	No (2)
Karlsson	1998	2	85 (2,3)	Children	-	-	-	-	-
Castro Lobera A	1999	2	180 (1,1)	Both	Goiter??	-	-	-	-
Sanz J	1999	3	-	Adults	-	Graves	-	PTU	I131 (2)
Ali FE	1999	1	58 (1,7)	Both	-	-	-	-	I131-
Gruneiro de Pappaandiek L	2002	4	137 (2,9)	Children	-	Graves	-	-	-
Soriano Guillen L	2003	3	-	Children	Goiter nervousness, tachycardia, weight loss	Graves	Cardiopathy	Metimazol	No
Dias VM	2005	1	169 (0,5)	Children	-	-	-	-	-
Ahluwalia	2005	1	-	Children	Irritability, weight loss	-	Carbimazol	-	-
Chemli J	2006	1	-	Children	Diarrhea. Delayed onset of puberty	-	Celiac disease	-	-
Sahin M	2006	1	1 case	-	Goiter	Graves	-	Carbimazol	Subtotal thyroidectomy

cases of hyperthyroidism were caused by Graves disease. This confirms the importance of autoimmune disorders in DS. Celiac disease and atopia were the other autoimmune disorders most frequently associated with hyperthyroidism. There was no hyperthyroidism secondary to other autoimmune conditions such as hashitoxicosis, which has been described in isolated cases (26). The absence of spontaneous remission or a shift to hypothyroidism makes it highly unlikely that any such potential condition might have been misdiagnosed as Graves disease. Beyond that, no cases of hyperthyroidism were found to have been caused by overtreatment of primary hypothyroidism. The majority of our study population, it must be pointed out, comes from an area where goiter is not endemic; this may partly explain the lack of hyperthyroidism caused by toxic multinodular goiter.

Ophthalmopathy had a prevalence of 16%, which is lower than the 25% rate of Graves ophthalmopathy for the general population at the time of diagnosis (27), although much higher rates are found when using specific imaging techniques such as CT scans or orbital MRI. The reason for this may lie with the fact that our population is younger or the fact that none were smokers. Specific imaging techniques such as orbital MRI were not used, as most patients lacked apparent exophthalmos. We cannot therefore rule out the possibility that routine specific eye imaging might have found a higher rate of ophthalmopathy. In any case, we found no clinically relevant cases.

In our experience, the clinical features of hyperthyroidism among patients with DS are similar to those for the general population, except for a younger age at the time of diagnosis and a more even gender distribution. Hyperthyroidism may have an impact on growth and development of children and adolescents. Accelerated growth goes hand in hand with accelerated maturation of the epiphyseal plate. Accelerated growth may be subtle, and depends on the duration of the condition prior to diagnosis. Table III shows that the majority of patients were in the 3rd percentile or lower, relative to the general population, but we must also bear in mind that DS per se is a cause of low height, particularly during childhood and adolescence. A comparison to DS growth tables shows that 8 out of 12 patients with hyperthyroidism were in the 50th percentile or higher, so the impact on height in this particular series seems minimal. Weight percentiles compared to the population with DS also appear to fail to drift to the lower bounds. Height and short-term accelerated linear growth require no intervention; generally, antithyroid drug treatment brings growth rate and bone age close to normal. In an Italian study of 101 children with Graves disease, where bone age was advanced at the time of diagnosis, adult height reverted to normal after treatment with antithyroid drugs (28). The effect of hyperthyroidism in puberty is not very well known, but it appears that as long as the duration of the condition is brief, negative effects are minor (29). Pubertal growth may be delayed, and when it has already started, may slow down until treatment is initiated.

The high prevalence of hypothyroidism among people with DS is evidenced in a number of studies (6, 7, 30, 31). Early screening programs have therefore been promoted for purposes of early detection. The American Academy of Pediatrics recommends an evaluation of thyroid function at 6 and 12 months, and subsequently on a yearly basis (3). Although such screening is effective for hypothyroidism, the findings of the present study show that it is not generally effective at finding hyperthyroidism at an early stage in DS. In the natural history of hypothyroidism, clinical disease has an insidious onset after a long period of subclinical hormonal imbalance, whereas hyperthyroidism due to Graves disease usually has a more sudden onset that is not usually preceded by a subclinical stage detectable in laboratory tests. Thus, unlike hypothyroidism, where clinical symptoms are less significant because they are unspecific and because many of them overlap with those of DS, a diagnosis of hyperthyroidism should be grounded on suspicions based on typical clinical manifestations (sweating, weight loss, palpitations, etc.), and requires biochemical confirmation for purposes of early diagnosis. Still, some authors have described asymptomatic and atypical forms of Graves disease (32), and it is not unheard-of for a diagnosis to be made in the context of a screening test for hypothyroidism.

Once a diagnosis has been established, treatment should be decided on the basis of a number of considerations. Options available are the same as for the general population: medical treatment, radioiodine, or surgery. Most authors recommend medical treatment with antithyroid drugs initially, tapering dosage down to withdrawal. If clinical remission ensues, permanent treatment will not be required. In our study, 100% of cases required permanent treatment. A recent prospective multicenter study carried out in France with 154 children treated for Graves disease with carbimazol showed a higher risk of recurrence in non-Caucasians and in patients whose TSI and L-T4 antibody levels were highest at the time of diagnosis. Risk of recurrence subsided with age and with achievement of a longer euthyroid period with the first course of antithyroid drugs (33). The choice of radioiodine versus surgery depends on the physician's personal experience and the patient's own specificities. In our study, permanent treatment with iodine-131 was prescribed for all patients except where their families rejected it. Patiens treated in this way had no side-effects, and ophthalmopathy did not become worse in any of these cases, although it must be admitted that the majority had no clinical ophthalmopathy at the time of diagnosis. Surgery was not performed on any of the patients. The choice of surgery versus radioiodine is controversial due to a lack of consensus,

although iodine may have some benefits compared to surgery, as it does not require hospitalization and is more comfortable for the patient. Moreover, patients with DS have some craniofacial abnormalities leading to a higher incidence of obstructive airway conditions, which can pose a challenge in surgery during induction of anesthesia or in an emergency. Furthermore, shorter necks may entail a greater surgical risk in thyroidectomy. Still, surgery is the quickest way to achieve euthyroid status, and in the hands of an experienced surgeon is a safe and effective method to eradicate hyperthyroidism. Sahin et al described a case of Graves-Basedow disease in a patient with DS who was subjected to a successful partial thyroidectomy (34). Surgery may be the treatment of choice when patients are too young for iodine-131, develop toxic reactions to antithyroid drugs, have overly large goiter, or need a quick end to their thyrotoxic status. Rivkees et al carried out a metaanalysis of surgical complications in 2,000 children and found temporary hypocalcemia in 10%, hypoparathyroidism in 2%, paralysis of the recurrent nerve in 2%, and death in < 0.1% (35). At any rate, our own experience with iodine-131 was satisfactory in every case, with no incidents worth noting.

Conclusions

The results of our study lead us to conclude that among the thyroid conditions associated with DS, hyperthyroidism is less frequent than hypothyroidism, and its etiology in the majority of cases is Graves disease. This condition may have an impact on growth and pubertal development. Early diagnosis and treatment are important, but annual biochemical screening is not of use. Hence, clinical suspicion is of the essence in terms of arriving at a relatively swift diagnosis. Spontaneous remission is not a frequent occurrence, and permanent treatment becomes necessary in practically every case.

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