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ORIGINAL ARTICLE

Hyperthyroidism in a population with Down syndrome (DS)

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Summary

Background Thyroid disorders are frequent in patients with Down syndrome (DS). It is well-known that the prevalence of hypothyroidism is high but data on hyperthyroidism are scarce.

Objectives To assess the prevalence, aetiology, clinical characteristics, evolution and treatment of hyperthyroidism in a population with DS attending a specialized medical centre.

Methods Data were gathered by systematic review of 1832 medical records from the Catalan DS Foundation, in Spain, registered between January 1991 and February 2006. Patients with the diagnosis of hyperthyroidism were identified and data on clinical features, physical examination, laboratory and imaging tests, treatment and evolution were collected.

Results Twelve patients with hyperthyroidism were recorded (6·5 cases/1000 patients with DS). There were 5 males and 7 females, with a mean age at diagnosis of 16·8 years. The most common presenting symptoms were decreased heat tolerance, sweating, increased irritability and weight loss. All patients had diffuse goitre at physical examination and two patients presented with exophthalmia. Clinical diagnosis was confirmed biochemically. Thyroid-stimulating immunoglobulin levels were raised (mean 128·1 U/l) and imaging tests confirmed the diagnosis of Graves' disease in all cases. Patients started treatment with carbimazole at diagnosis and after a mean period of 40 months without clinical remission, they required definitive therapy with radioactive iodine. Subjects developed hypothyroidism after radio-iodine therapy and replacement therapy with levothyroxine was necessary.

Conclusions Hyperthyroidism is more prevalent in patients with DS than in the general population and has no gender predominance. It is caused mainly by Graves' disease. Anti-thyroid drugs were not effective in achieving remission and radioactive iodine as a definitive treatment was required in all cases.

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Introduction

Down syndrome (DS) is the most common chromosomal disorder associated with mental deficiency. The incidence of DS varies between 1/449 and 2/700 of live births according to studies carried out in different countries.[1] DS is frequently associated with other disorders.[2,3]

Thyroid disorders are more frequent among children[4–7] and adults[8,9] suffering from DS than in the general population. Hypothyroidism is the most common form of thyroid disorder associated with DS, with a prevalence close to 50%.[10,11] Hyperthyroidism could also be more prevalent than in general population although only sporadic cases have been reported in the literature.[4,12]

The objective of this study was to assess the prevalence, aetiology, clinical characteristics, associated pathology, treatment and evolution of hyperthyroidism in a population with DS attending a specialized medical centre.

Patients and methods

Data were gathered by systematic review of 1832 medical records from the Catalan DS Foundation, in Spain, registered between January 1991 and February 2006. All patients in the database with the diagnosis of hyperthyroidism were identified. Subjects were all evaluated by the same endocrinologist.

The Catalan Down Syndrome Foundation (FCSD) is a nonlucrative organization established in 1984. The objective of FCSD is to promote the complete development of persons with DS. The Foundation provides support from prenatal diagnosis until adult age. The medical team provides a preventive health programme that includes thyroid function screening on a yearly basis. The FCSD does not include a complete register for all patients with DS in Catalonia.

When hyperthyroidism was diagnosed, the following variables were collected: age, anthropometric measures, clinical characteristics (palpitations, insomnia, decreased heat tolerance, profuse sweating, nervousness, hyperdefaecation, distal tremour, weight loss), physical examination including thyroid gland, eyes and heart rate, laboratory determinations: TSH, free T4, total T3, thyroid peroxidase autoantibody (anti-TPO), thyroglobulin autoantibody (anti-Tg), and thyroid-stimulating immunoglobulin. Family history of thyroid disorders and presence of other autoimmune disorders were registered. Technetium^{99} scintigraphy was performed in all patients, and thyroid

ultrasound was indicated in selected cases according to the physician in charge. Patients were re-assessed at 2-month intervals.

Results

Out of the 1832 subjects with DS who attended the FCSD between January 1991 and February 2006, 12 (5 males and 7 females) were diagnosed of hyperthyroidism. Therefore, the prevalence of hyperthyroidism in this DS population was 6·5 cases/1000 subjects with DS. The estimated incidence is 43,67/100·00 per year.

The mean age at diagnosis of hyperthyroidism was 16·8 years (range 10·9–28·9 years), with a mean weight of 42·5 kg (range 24·5–68·8 kg) and a mean height of 142·6 cm (range 123·4–153 cm). Six months after treatment was initiated, there was a mean weight gain of 11·4 kg and an average increase in height of 5·3 cm during the first 6 months after treatment.

All patients were diagnosed clinically, not during the yearly thyroid function screening included in the health program for people with DS. At the time of diagnosis, 11 patients complained of decreased heat tolerance and sweating, 10 had increased irritability, 10 lost weight in the previous months [average lost of 4·7 kg (range 1–10 kg)], 9 suffered from palpitations, 7 had insomnia, 7 showed distal tremour, 4 had increased bowel frequency, and 3 patients complained of sore eyes. The mean heart rate at diagnosis was 93·9 beats per minute (range 80–132), thyroid examination revealed a diffuse goitre in all patients (11 cases of grade 2, 1 case of grade 3, according to the WHO semiological/Clinical classification) and 2 patients presented with exophthalmos. There were no cases of pretibial myxedema.

Clinical features of the study population are summarized in Table 1.

With regard to results of laboratory tests, all patients had an undetectable TSH, with elevated free T4, average 63·7 pmol/l (range 24·5–158·6 pmol/l) (normal range 9–19·4 pmol/l), total T3 11·2 nmol/l (range 2·8–22·8 nmol/l) (normal range 1·2–2·5 nmol/l). All patients had increased serum thyroid-stimulating immunoglobulin concentrations with a mean value of 128·1 U/l (range 10–620 U/l) (normal range < 10 U/l). Anti-TPO were present in 92% (11/12) and anti-TG in 33·3% (4/12) of patients. Almost all patients showed positivity for at least two markers of thyroid autoimmune disease.

Technetium^{99} scintigraphy showed diffuse uptake in all patients, suggesting the diagnosis of Graves' disease. Only two patients had a thyroid ultrasound performed, and it revealed a diffuse goitre without nodules.

Treatment with carbimazole was started in all patients at the time of diagnosis. An initial dose of 10 mg three times daily was administered. Further adjustments on total daily dose were made based on periodic thyroid function assessments until definitive therapy was done. No patient experienced adverse events due to carbimazole, such as cutaneous rash, leucopenia or agranulocytosis. Carbimazole withdrawal was attempted in all cases but no patient achieved remission longer than 6 months. Radioiodine was indicated when patients relapsed or after more than 24 months without carbimazole withdrawal. Information to parents or guardians was given regarding risks and benefits of radioiodine before gaining informed consent. Although the patients would not have had the mental capacity to make such a decision, they were also informed in terms understandable for them.

Patients underwent definitive therapy with Iodine 131 following a mean period of medical treatment of 40·3 months (range 10–96 months). Only two patients underwent continued treatment with carbimazole because of family refusal to treatment with radioactive iodine. All patients developed hypothyroidism after radioiodine therapy and required definitive replacement therapy with levothyroxine.

As for associated disorders, two patients had been diagnosed of congenital heart defects. Other autoimmune disorders found in hyperthyroid patients were coeliac disease (2 cases), myasthenia

Table 1. Clinical features of the twelve DS patients with hyperthyroidism

	Gender	Age at diagnosis (years)	Aetiology	T4L at diagnosis (pmol/l*)	TSI	Thyroid antibodies†	Other pathologies	Goitre	Ophthalmopathy	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		+	–	–

TSI, thyroid stimulating immunoglobulin. *Normal range 9·0–19·4 pmol/l, †anti-TPO or anti-Tg.

Table 2. Hyperthyroidism and Down Syndrome. Bibliographical review

Author	Year	Cases	Screened population (prevalence%)	Population	Clinical characteristics	Aetiology	Associated disorders	Initial treatment	Definitive treatment
Hollingswoth DR[14]	1974	2	60 (3,3)	Both	Goitre, Exophtalmus	–	–	–	No
Baxter RG[9]	1975	1	11 (2,9)	Adults	–	–	–	Carbimazole	–
Murdoch JC[8]	1977	1	82 (1,2)	Adults	–	–	–	–	–
Fort P[4]	1984	3	121 (2,5)	Children	–	Graves'	–	–	–
Pueschel SM[13]	1985	0	151 (0)	Both	–	–	–	–	–
Loudon[12]	1985	1	116 (0,8)	Children	–	–	–	–	–
Cutler A[7]	1986	1	49 (2)	Children	Failure to thrive	Graves'	–	PTU	No
Zori RT[11]	1990	5	61 (2,3)	Both	–	3 Thyroiditis 2 Graves'	Gastric atrophy	–	–
Dinani[15]	1990	1	106 (0,9)	Adults	–	–	–	–	–
Pozzan[16]	1990	2	108 (2)	Both	–	Graves'	–	–	–
Pueschel SM[17]	1991	1	181 (0,5)	Children	No	–	–	–	–
Colombo ML[5]	1992	1	45 (0)	Both	No	Transient	Cardiopathy	–	–
Selikowitz M[18]	1993	0	101 (0)	Children	–	–	–	–	–
Tambyah PA[19]	1993	2	–	Adults	–	Graves'	–	–	–
Sridhar GR[20]	1997	1	–	Children	–	–	–	–	–
Bhowmick[21]	1997	5	–	Children	–	Graves'		PTU	No (2)
Karlsson[22]	1998	2	85 (2,3)	Children	–	–	–	–	–
Castro Lobera A[23]	1999	2	180 (1,1)	Both	Goitre?	–	–	–	–
Sanz J[24]	1999	3	–	Adults	–	Graves'	–	PTU	^{131}I (2)
Ali FE[25]	1999	1	58 (1,7)	Both	–	–	–	–	^{131}I
Gruneiro de Pappaandiek L[6]	2002	4	137 (2,9)	Children	–	Graves'	–	–	–
Soriano Guillen L[26]	2003	3	–	Children	Goitre, nervousness Tachycardia, weight loss	Graves'	Cardiopathy	Metimazole	No
Dias VM[10]	2005	1	169 (0,5)	Children	–	–	–	–	–
Ahluwalia[27]	2005	1	–	Children	Irritability Weight loss	–	–	Carbimazole	–
Chemli J[28]	2006	1	–	Children	Diarrhoea Delayed puberty	–	Coeliac disease	–	–
Sahin M[29]	2006	1	Case report	–	Diffuse goiter tachycardia	Graves'	–	Carbimazole	Subtotal thyroidectomy

gravis (1 case), vitiligo (1 case) and alopecia areata (1 case). There were no cases of type 1 diabetes. In total, four patients had an associated autoimmune disease (33%).

Discussion

Individuals suffering from DS show a higher prevalence of autoimmune disorders than the general population,[2,3] in particular, thyroid disorders.[4,13] The most frequent thyroid disease is hypothyroidism for which a prevalence ranging from 20% to 50% has been reported.[11,12] Most studies on thyroid function in DS population show a low prevalence of hyperthyroidism,[4,12] generally under 3%, although this prevalence is clearly higher than that of the general population. As far as we are aware, this is the largest series of subjects with DS and hyperthyroidism reported in the literature (Table 2) and reveals an autoimmune aetiology in all cases. This study confirms the increased incidence (43/10 000 per year) and prevalence (6·55/1000) of hyperthyroidism in the DS population. For comparison, data available about the rate of hyperthyroidism in Spain reports an incidence of Graves' disease of 24·24 per 100 000 per year.[30] Epidemiological data about thyrotoxicosis in young people are scarce. In a Danish study, incidence of thyrotoxicosis in juvenile people was 0·79/100 000 person.year, with a clear female preponderance of 6·7 : 1.[31]

Clinical characteristics of hyperthyroidism in DS patients are similar to those found in the general population with the exception of young age at diagnosis and no female predominance.

In all cases, the diagnosis was based on a high degree of clinical suspicion, and confirmed biochemically, rather than in the yearly thyroid function screening program. A possible explanation for this finding could be that hyperthyroidism usually has an acute presentation, in contrast to the insidious course of autoimmune hypothyroidism.

Patients with DS have a high prevalence of autoimmune disorders,[7,11] particularly thyroid autoimmune disease. Almost 30% of DS population has raised levels of antithyroid antibodies[11] and its presence is clearly associated with hypothyroidism. As for hyperthyroidism, although only sporadic cases have been described in the literature,[4,7,11,12,14–29] the most frequent cause being Graves' disease. In fact, in the present series, all cases were due to Graves' disease. The prevalence of ophthalmopathy of 16%, however, was lower than that reported for the general Graves' population, which may be due to young age or the fact that none of the subjects were smokers.

There were no cases of hyperthyroidism due to other autoimmune disorders such as hashitoxicosis, although a single case has been reported.[24] There could have been cases of hashitoxicosis misdiagnosed as Graves' disease, nevertheless, the lack of spontaneous remission or evolution to hypothyroidism makes this circumstance extremely unlikely. No cases of hyperthyroidism caused by over-treated primary hypothyroidism were detected.

In the present study, definitive therapy with Iodine-131 was prescribed for all patients, except for those whose family refused this option. Patients that underwent iodine treatment did not develop any side-effects and, in particular, there were no cases of deterioration of ophthalmopathy after radioiodine.

No patient underwent surgery as definitive therapy, although Sahin *et al.*[29] reported a case of Graves' Basedow disease in a patient with DS successfully treated with subtotal thyroidectomy. There is a lack of consensus on the role of thyroidectomy in the treatment of Graves' disease in DS patients, but radioiodine treatment offers several advantages over surgery. DS patients present certain craniofacial anomalies that lead to a higher incidence of obstructive airway problems, such as difficulties during anaesthetic induction. Also, these patients, because of their short necks, may present a surgical risk for thyroidectomy. The role of surgery in these patients should probably be limited for those suffering serious side-effects of antithyroid drugs or for those who require a rapid termination of the thyrotoxic state.[29]

Salient characteristics of hyperthyroidism in subjects with DS can be summarized as follows: (i) onset of symptoms between late childhood and early adulthood, (ii) no sex predominance, (iii) autoimmune aetiology in all cases, and (iv) definitive treatment always required in this cohort.

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