There is an increased incidence of hyperthyroidism in Down syndrome that should be regularly tested for at all ages

Goday-Arno A, Cerda-Esteva M, Flores-Le-Roux JA, Chillaron-Jordan JJ, Corretger JM, Cano-Perez JF. Hyperthyroidism in a population with Down syndrome (DS). Clin Endocrinol (Oxf) 2009;71:110-4.

SUMMARY

BACKGROUND Hypothyroidism is the most common thyroid abnormality in Down syndrome (DS), with a prevalence of almost 50%; however, whether hyperthyroidism might be more prevalent than usual in DS is unknown, as only sporadic cases of hyperthyroidism with DS have been reported in the literature. The aim of this study was to assess the prevalence, cause, clinical characteristics, pathology, treatment, and evolution of hyperthyroidism in a population with DS.

METHODS This is a retrospective study of 1832 medical records from the Catalan Down Syndrome Foundation in Spain, from which data for the study cohort were obtained from January 1991 through February 2006. The records contained the following information: patient age, anthropometric measurements, clinical symptoms and signs of hyperthyroidism such as insomnia, decreased heat tolerance, profuse sweating, nervousness, hyperdefecation, and weight loss. In addition, the findings on physical examination included the thyroid examination, heart rate, eye signs of hyperthyroidism, and distal tremor. Laboratory information was available concerning the serum thyrotropin (TSH), serum free thyroxine (FT_4), total triiodothyronine (T_3), serum thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb), and thyroid-stimulating immunoglobulin (TSI). Family histories of thyroid disorders and other autoimmune disorders were also obtained. All patients with hyperthyroidism had a technetium-99m (99mTc) thyroid scan, and some had a neck ultrasound examination, depending on the attending physician. Patients with hyperthyroidism were reassessed at 2-month intervals.

RESULTS Among 1832 individuals with DS, 12 had hyperthyroidism, 5 of whom were male and 7 of whom were female, with ages ranging from 10.9 to 28.9 years. The mean weight was 42.5 kg (93.5 lb; range, 24.5 to 68.8 [53.9 to 151.4]), and the mean height 142.6 cm (56.1 in.; range, 124.4 to 153 [49 to 60.2]).

DIAGNOSIS The diagnosis of hyperthyroidism was made clinically, and not as a consequence of thyroid-function screening tests that were performed annually in all individuals with DS. Symptoms leading to a diagnosis of hyperthyroidism were decreased heat tolerance and sweating (n = 11, 92%), increased emotional irritability (n = 10, 83%), a mean weight loss of 4.7 kg (25.1 lb) in the previous months (n = 10, 83%), palpitations (n = 9, 75%), insomnia (n = 7, 58%), distal tremor (n = 7, 58%), increased bowel frequency (n = 4, 33%), and sore eyes (n = 3, 25%). Mean heart rate at the time of diagnosis was 94 beats/min (range, 80 to 132) (Figure 1). The thyroid examination revealed diffuse thyroid enlargement in all the patients, which, according to the World Health Organization criteria, were grade 2 goiters in 11 patients and grade 3 in 1 patient (Figure 2). Two patients (17%) presented with exophthalmos.

LABORATORY TESTS All patients had undetectable serum TSH concentrations with elevated median serum FT_4 concentrations of 63.7 pmol/L (4.93 ng/dl), with a range of 24.5 to 158.6 (1.89 to 12.3; reference range, 9 to 19.4 pmol/L [0.69 to 1.51 ng/dl]), and elevated mean serum total T_3 concentrations of 11.2 nmol/L (727 ng/dl), with a range of 2.8 to 22.8 (182 to 1480; reference range, 1.2 to 2.5 [77.9 to 162]). Mean serum TSI concentrations were increased to 128.1 U/L (range, 10 to 620; reference range, <10 IU/L]). TPOAb elevations were present in 11 of 12 patients (92%), and serum TgAb elevations were found in 4 of 12 patients (33.3%).

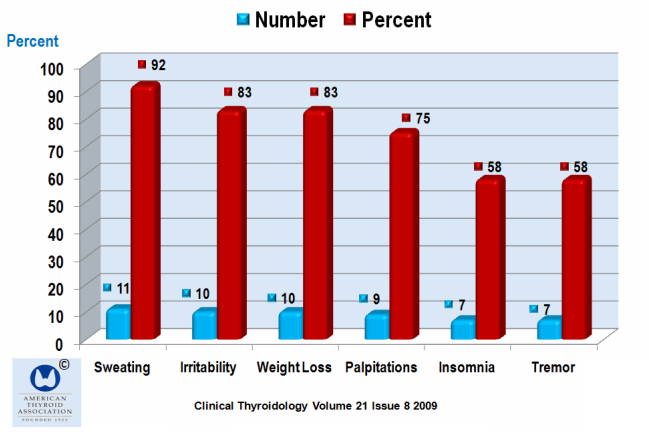

Figure 1. This figure shows the main symptoms of hyperthyroidism in patients with Down Syndrome

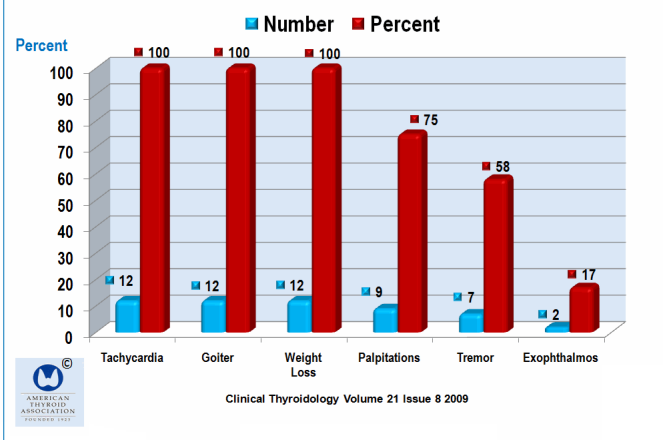

Figure 2. This figure shows the main physical findings of hyperthyroidism in patients with Down Syndrome

A 99mTc scan showed diffuse thyroid uptake in all patients, which was suggestive of Graves' disease. A diffuse goiter was found in the two patients who had neck ultrasonography.

EPIDEMIOLOGY The incidence of Graves' disease in the DS population was 43 cases per 10,000 persons per year, as compared with 24 cases per 100,000 persons per year in the population of Spain. In a Danish study, the incidence of juvenile thyrotoxicosis was 0.79 per 100,000 persons. All were lower than the incidence rates of Graves' disease in the DS population

TREATMENT For all patients, the initial therapy was 10 mg of carbimazole three times daily, which was adjusted according to the results of thyroid-function tests. Carbimazole withdrawal was attempted in all patients, but all experienced a relapse. After a mean of 40.3 months (range, 10 to 96) only 2 patients continued to take carbimazole, because their families rejected treatment with radioactive iodine (^{131}I). After relapse, the other 10 patients were treated with ^{131}I, which resulted in hypothyroidism requiring levothyroxine therapy in all patients.

OUTCOME During the first 6 months of therapy, the mean weight increased by 11.4 kg (3.1 lb) and the mean height by 5.3 cm (21 in.). Among the patients with hyperthyroidism, 2 had celiac disease, and there was 1 case each of myasthenia gravis, vitiligo, and alopecia areata. There were no cases of diabetes mellitus.

CONCLUSION There is an increased incidence of hyperthyroidism in DS that often fails to achieve remission with antithyroid drugs, subsequently requiring radioiodine treatment.

COMMENTARY

DS is the most common genetic form of mental retardation and the leading cause of certain birth defects and medical conditions (1). The association of DS with thyroid disorders has been recognized for decades. Over 25 years ago, reports (2) described overt thyroid dysfunction in DS. At present, up to 54% of individuals with DS are reported to have thyroid disorders, the prevalence of which increases with age (3). However, most of the literature has focused on hypothyroidism in DS, which has consequently resulted in the recommendation to regularly screen individuals with DS for hypothyroidism (4). However, Goday-Arno found 27 articles in the literature from 1974 through 2005 that reported a total of 46 cases of hyperthyroidism in DS. Among this group, Graves' disease was documented in 10 cases, while the cause was uncertain in the other 17. In seven of the articles, carbimazole and propylthiouracil were used to treat hyperthyroidism, but the details of drug therapy were not described in the others. Only 2 patients were treated with ^{131}I and 2 had subtotal or total thyroidectomy.

A much clearer picture emerges in the group of patients with DS described by Goday-Arno et al. All cases of hyperthyroidism were due to Graves' disease. Only 16% of the patients had ophthalmopathy, a rate lower than that reported for the general population with Graves' disease. The authors suggest that this may be the result of the young age of many of the patients in this study and the fact that none were smokers. Otherwise, the clinical characteristics of Graves' hyperthyroidism in the patients with DS had features of hyperthyroidism that were similar to those found in the general population with Graves' disease.

Why none of the patients in the study achieved remission with antithyroid drugs is not entirely clear, but in contrast to the usual insidious onset of autoimmune hypothyroidism, the cases reported by Goday-Arno had overt thyrotoxicosis at the time of diagnosis, with obvious symptoms and overt biochemical features of hyperthyroidism. Still, the most striking feature of these cases is that none of the 12 patients responded to carbimazole or propylthiouracil despite being on antithyroid drugs for as long as 96 months. After an average of 40 months on antithyroid drugs, all of the patients failed to achieve remission and all but 2 were thus treated with ^{131}I. The 2 patients not so treated remained on antithyroid drugs because the parents did not want their children treated with ^{131}Iand none were treated with surgery. Almost 30% of the DS population has high levels of antithyroid antibodies (5), but there were no cases of hyperthyroidism due to autoimmune disorders, commonly referred to Hashitoxicosis. Yet, among the patients with hyperthyroidism, there were 2 cases of celiac disease and 1 case each of myasthenia gravis, vitiligo, and alopecia areata, without any cases of diabetes mellitus.

The major finding in this study is that the incidence of hyperthyroidism among individuals with DS is significantly greater than that in the general population, underscoring that physicians must be aware of the problem and perform thyroid-function tests at all ages in patients with DS.

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References

1. Sherman SL, Allen EG, Bean LH, et al. Epidemiology of Down syndrome. Ment Retard Dev Disabil Res Rev 2007;13:221-7.

2. Fort P, Lifshitz F, Bellisario R, et al. Abnormalities of thyroid function in infants with Down syndrome. J Pediatr 1984;104:545-9.

3. Cohen WI. Current dilemmas in Down syndrome clinical care: celiac disease, thyroid disorders, and atlanto-axial instability. Am J Med Genet C Semin Med Genet 2006;142C:141-8.

4. Van Cleve SN, Cannon S, Cohen WI. Part II: Clinical practice guidelines for adolescents and young adults with Down syndrome: 12 to 21 years. J Pediatr Health Care 2006;20:198-205.

5. Zori RT, Schatz DA, Ostrer H, et al. Relationship of autoimmunity to thyroid dysfunction in children and adults with Down syndrome. Am J Med Genet Suppl 1990;7:238-41.