Thyroid Disorders in Down Syndrome

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Abstract

Thyroid dysfunctions are important among the conditions associated with Down Syndrome (DS), due to their high prevalence and to their potential impact on quality of life. That is why routine TSH, T4 and T3 determination must be carried out at regular intervals on all patients with DS.

Hypothyroidism is common in DS patients, and levothyroxine replacement therapy must be started if TSH levels exceed 10 mcU/mL, T3 or T4 levels are low, or antithyroid antibody titres are high. A need for cardiac surgery is also an indication. It is advisable to start with a low-dose treatment (12.5 µg/day) and then adjust it until TSH levels have been normalized.

Slight and usually transitory minor subclinical hypothyroidism is a common occurrence in the first three years of life, and the need for treatment with levothyroxine is to a certain extent disputed. In this respect, a recent clinical trial showed an improvement in terms of psychomotor development in a group of patients treated with levothyroxine from the neonatal period. Follow-up in the trial was carried out for 24 months, and the improvement in psychomotor development was estimated at 0.7 months, while allowing for the possibility of magnified differences in subsequent checks.

Regarding hyperthyroidism in DS, although it arises in a higher percentage than among the general population, it has a much lower incidence than hypothyroidism. The most frequent etiology is toxic diffuse goitre, or Graves-Basedow disease, which is initially treated with synthetic antithyroids (methimazole or carbimazole) and beta-adrenergic blocking agents (propranolol or atenolol). Where hyperthyroidism persists, a definitive treatment must be considered, preferably with radioiodine, given the advantages it offers over surgery (with its attendant hospital stay, anaesthesia, and so on.).

Keywords: Diabetes mellitus. Hyperthyroidism. Hypothyroidism. Obesity. Low height.

Introduction

Thyroid dysfunctions are important among the conditions associated with Down syndrome (DS), as they are highly prevalent (1) and may have a considerable impact on quality of life. It is therefore fundamental for the key aspects of screening, diagnosis, clinical course and treatment to be known. Caring for patients with endocrine disorders is a significant share of the work in a dedicated medical centre that only caters for people with Down syndrome.
Hypothyroidism

Hypothyroidism is a highly prevalent condition among people with DS; it is certainly their highest-prevalence endocrine disorder (2-6). The overall rate of hypothyroidism in this population is estimated at 30% to 40% (1, 7), and may reach 80-90% in early childhood (7, 8). Published rates vary according to age group, inclusion of subclinical conditions in the definition, and whether routine thyroid screening is undergone by the whole study population (5). At Centre Mèdic Down (Down Medical Centre) run by Fundació Catalana Síndrome de Down (FCSD), out of a total of 1,600 case histories and 367 patients with DS seen in our endocrinology clinic, we found hypothyroidism (whether clinical or subclinical) in 38% of patients (8).

The well-known signs and symptoms of hypothyroidism include asthenia; cold intolerance; dry, coarse or cold skin; constipation; drowsiness; apathy; weight gain; changes in voice quality; macroGLOSSIA; and others. However, in our experience, focused history taking and physical examination are of little value when diagnosing hypothyroidism associated with DS. One reason is that patients with DS and normal thyroid function often have some typical signs and symptoms of clinical hypothyroidism, such as dry, coarse skin, macroGLOSSIA, apathy, or a tendency to gain weight. Even when we systematically take the patient's history and go through the symptoms and signs classically used in a diagnostic scoring system, patients with thyroid dysfunctions have the same scores as those without. More practically, searching for signs and symptoms of hypothyroidism tends to be of little value because we usually diagnose it at the subclinical stage, long before the typical myxedema clinical constellation develops. This is because the natural history of hypothyroidism begins with a subclinical phase in which only thyrotropin (TSH) levels are elevated. This is followed by a phase in which there is a drop in thyroid hormone levels, both thyroxine (T4) and triiodothyronine (T3).

Given the high prevalence of hypothyroidism in DS, the ability to screen for it by measuring TSH levels, and the effectiveness of treatment, the CMD general health program includes routine biennial TSH measurement. Thus, practically all patients with hypothyroidism have been diagnosed at a subclinical stage, before developing the typical symptoms and signs.

There are two diagnostic categories of hypothyroidism in DS:

- Subclinical hypothyroidism: The early stage, with elevated TSH levels but normal T4 and T3 levels.

There are no signs or symptoms of low thyroid function at this stage, by definition.

- Clinical hypothyroidism: The advanced stage of the disease, with elevated TSH levels and a drop in T4 and T3 levels. By definition, the signs and symptoms of low thyroid function do appear at this stage.

As pointed out above, the great majority of patients with DS enrolled in a DS-specific health program are diagnosed at the subclinical stage, in which elevated TSH is the only detectable sign.

The main diagnostic test for hypothyroidism in DS is TSH measurement, with T4 and T3 levels measured either conditionally or routinely. In the routine clinical workup to diagnose a primary thyroid dysfunction, the pathophysiology of the hypothalamic-pituitary-thyroid axis and its negative-feedback control mean that normal TSH levels rule out both primary clinical or subclinical hypothyroidism (which raises TSH) and clinical or subclinical hyperthyroidism (which suppresses TSH). Therefore, if TSH is normal there is no need to measure T4 or T3, as they will necessarily be normal, too. Many analytical laboratories in the public health care system therefore only measure T3 and T4 levels from the same serum sample if TSH is abnormally high or low. Normal TSH rules out thyroid dysfunction by itself; T4 and T3 are not required.

However, this algorithm does not apply if a pituitary disorder is suspected. TSH may then be «inappropriately» normal concomitant with low T3 or T4 levels (secondary hypothyroidism) (9). Pituitary disorders are far less prevalent than primary thyroid disorders. Additionally, while people with DS have a higher prevalence of primary hypothyroidism, pituitary disorders are just as prevalent as among the general population. Therefore, measuring TSH first and only conditionally determining T3 and T4 levels is also an appropriate strategy for DS. However, the conditional T4 and T3 measurements should always be performed on the same serum sample, from a single extraction. It is often technically difficult to obtain blood from patients with DS, especially children or very agitated individuals. It would be unforgivable in these cases for our diagnostic strategy to require a second extraction depending on the test results of the first. When in doubt, therefore, it makes sense to screen directly for TSH, T4, and T3 if the patient has DS.

Testing for antithyroid, antiperoxidase and antithyroglobulin antibodies can detect autoimmune diseases attacking the thyroid gland. Autoimmune destruction of the thyroid is one of the most frequent causes of hypothyroidism, so it should be tested for once clinical or subclinical hypothyroidism has been established, to determine whether it is an autoimmune condition. Besides, a positive test for antithyroid
antibodies predicts greater likelihood of progression from the subclinical stage to the clinical stage (35% in some series). Thus, antibodies only test positive in some cases of subclinical hypothyroidism.

(6, 10-13).

Ultrasound is the preferred thyroid imaging technique. However, with DS, there is no need to obtain a thyroid sonogram for either clinical or subclinical hypothyroidism. Careful palpation of the neck will usually suffice to gauge the size of the thyroid gland. In our own clinical practice we only request a sonogram if palpation points to goiter or nodules.

At any rate, ultrasound imaging is harmless and readily accessible, so it should be performed whenever there is any doubt.

Conversely, thyroid scintigraphy, a classic thyroid imaging technique, provides no relevant information in cases of hypothyroidism and DS, so we consider it inadvisable.

**Treatment protocol**

The preferred treatment for hypothyroidism in DS is oral levothyroxine sodium replacement therapy. Patients should be started on a very low dose which is gradually increased while monitoring TSH, T4 and T3 levels until TSH is normal (11). The replacement dose will vary from 2 to 5 micrograms/kg/day. Our own experience with 48 patients aged 5 to 15 is that the usual daily dose range is 25 to 75 µg.

A good range of levothyroxine sodium presentations are currently available in Spain; tablets are available in 25, 50, 75, 100, 125, 150, 175 and 200 µg. The starting dose should be 12.5 µg for children and 25 µg for adults.

The main question when treating hypothyroidism in DS is when to begin treatment, especially when it is a mild subclinical case (10). If the condition is clinical there is no doubt as to the need to initiate replacement therapy. However, most cases are detected by routine screening at a subclinical stage (12), and there is a historical controversy as to when treatment can begin in such patients (11). The following are unanimously accepted indications for starting treatment:

When TSH is more than twice the upper threshold of normality (higher than 10 mcU/mL; normal TSH < 5 mcU/mL). The alteration is then considered significant enough to initiate treatment.

When T3 or T4 levels lie below the lower threshold of normality: metabolically, the patient has reached the clinical stage.

When high-titre antithyroid antibodies are found alongside raised TSH levels. Hypothyroidism is more likely to progress to the clinical stage than if antibody tests are negative.

When the patient with DS needs heart surgery. Thyroid hormones are so important for heart physiology that thyroid function, it is felt, needs to be strictly normal before the operation.

**Subclinical hypothyroidism in early childhood**

Congenital hypothyroidism is also far more prevalent in people with DS than among the general population (2). Since there is a universal screening program in place for this condition in our area, newborns with DS are also screened, with nothing in particular to be noted.

The only special situation is when subclinical hypothyroidism is detected in children with DS in the first three years of life (8, 12, 14-17). In our experience with 57 children assessed for subclinical hypothyroidism before the age of 5 (61% boys, 39% girls), the mean baseline TSH level was 6.78 mcU/mL (normal < 5). In 91% of cases TSH was lower than 10 mcU/mL, with normal T4 levels in practically every case (98%). Only 14% were on levothyroxine. Therefore, just as in other series, subclinical hypothyroidism with DS is usually transient in early childhood and spontaneously reverts to normal after the age of two or three (17-20). This is similar to what is observed in preterm infants over the first three months. As a result, when TSH is slightly elevated with normal T3 and T4 levels in children aged up to 36 months, the traditional path of caution was to monitor hormone levels without providing treatment (18-20).

However, the results of a recently reported clinical trial are leading us to reconsider our choices when newborns with DS have a thyroid dysfunction (21).

This study -- an excellent one in terms of methodology, number of cases, study design and endpoints -- assessed the effects of routine L-thyroxine neonatal treatment compared to a placebo over the first two years of life for a total of 180 patients.

The primary endpoint was mental and motor development at age two, and the treatment group was shown to have a reduced delay in psychomotor development. The researchers started levothyroxine at 8 µg/kg/day before age 24 days for 99 patients, and compared them to 97 patients in the placebo group over 24 months’ follow-up. TSH and free T4 levels were measured every 6 months, and psychomotor development was assessed using BSID-II ("Bayley Scales of Infant Development Scale") and KID ("Kent Infant Development Scale") at 6, 12 and 24 months.
In the treatment group, free T4 remained within the upper normal range and TSH in the lower normal range. The difference compared to the placebo group was statistically significant. In terms of psychomotor development, psychomotor developmental delay at 24 months was greater in the placebo group; the estimated difference in developmental delay was 0.7 months. Size and weight were also higher in the treatment group, with statistically significant differences by age 6 months. Thus, length at 24 months in the treated group was 81.3±3.2 cm vs. 80.4±3.5 cm in the treatment group (p 0.046). Weight was 10.923±1.219 vs. 10.059±1.255 (p 0.022) (21).

Given the outcome of this study and the lack of side-effects, levothyroxine should be considered for diagnosed hypothyroid infants with DS.

While the differences between the treatment and control groups are statistically significant, they may be considered of little relevance in terms of clinical differences at 24 months. The authors of the study point out the possibility that such differences may become greater in subsequent follow-up testing, increasing their clinical significance. Moreover, given the lack of side-effects, any degree of clinical improvement might be considered effective; but this stance may be controversial.

Beyond this period, the status of most hypothyroid children and adults with DS on replacement therapy is permanent; generally speaking, there are no grounds to considere withdrawal of treatment unless there are well-founded suspicions concerning the validity of the original diagnosis.

Hyperthyroidism

Hyperthyroidism is more prevalent in DS than among the general population, but its incidence is far lower than that of hypothyroidism (3,4). The available literature merely consists of case report (22-25). As is the case with the general population, the most frequent etiology of an overactive thyroid gland with DS is toxic diffuse goiter. Less frequently, hyperthyroidism in DS may be caused by hashitoxicosis, a bout of hyperthyroidism in the context of chronic (Hashimoto) thyroiditis. In these cases, hyperthyroidism remits fairly soon and is followed by chronic hypothyroidism.

Although the health program at our center includes thyroid screening every two years, which is effective for hypothyroidism, early detection of hyperthyroidism in DS is not usually achieved in this way. This is due to the natural history of hyperthyroidism in Graves-Basedow disease: clinical onset is abrupt and is not preceded by a subclinical stage that can be detected. Unlike hypothyroidism in DS, in which the clinical picture is of little value, a diagnosis of hyperthyroidism needs to be suspected on clinical grounds: weight loss, insomnia, tachycardia, asthenia, etc. Therefore, a high level of alert for hyperthyroidism must be maintained for all people with DS. In a few cases, clinical manifestations may be rare and atypical; sometimes, the diagnosis is made on the basis of a screening test for hyperthyroidism. We have seen no cases of exophthalmos or infiltrative ophthalmopathy alongside hyperthyroidism caused by Graves-Basedow disease. However, dry eyes and eye itching are fairly frequent in people with DS.

General diagnostic protocol

First-line diagnostic tools

The fundamental diagnostic test for hyperthyroidism in DS is the measurement of TSH, T4 and T3 levels. Test results will show a characteristic pattern with suppressed TSH and clearly elevated T4 and T3 levels. Unlike hypothyroidism with DS, subclinical hyperthyroidism (suppressed TSH with normal T3 and T4 levels) is detected far less often.

Additional or complementary testing

Positive antithyroid antibodies, especially thyroid-stimulating immunoglobulin (TSI), as well as antiperoxidase and antithyroglobulin antibodies, will allow hyperthyroidism to be classified as autoimmune. As Graves Basedow disease is the most frequent cause of hyperthyroidism in DS, usually TSI levels will be high, with or without raised antithyroid antibody levels.

Contrary to what we recommend for hypothyroidism, thyroid scintigraphy may be of some use for hyperthyroid patients with DS. The characteristic pattern is the enhancing goiter typical of Graves-Basedow disease. However, if there are technical difficulties or if this technique is not readily available, it may be omitted with no significant implications for care. Scintigraphy offers clues as to etiology, to distinguish between Graves-Basedow disease and other causes such as toxic adenocarcinoma, toxic multinodular goiter, subacute thyroiditis, or factitious thyrotoxicosis. All of the hyperthyroidism cases seen at CMD were caused by the most frequent etiology: diffuse toxic goiter due to Graves-Basedow disease. The source population, it should be noted, generally comes from an area where goiter is not endemic (8). In endemic areas, toxic multinodular goiter is a frequent cause of hyperthyroidism.

Thyroid ultrasonography, which is harmless and
readily available, may be of use in gauging goiter size, although it can sometimes be misleading if incidental nodules or pseudonodules are seen.

**Treatment protocol**

Initial treatment for hyperthyroidism in DS is no different from that of the general population: synthetic antithyroid drugs (metimazole or carbimazole) and beta-adrenergic blockers (propanolol or atenolol), starting at full dosage and subsequently lowering dose levels according to clinical and hormonal improvement. If dosage can be tapered off completely and clinical remission is achieved, the patient will not require a definitive treatment (26). However, if remission is not achieved after a reasonable period of antithyroid treatment (9 months to a maximum of 2 years), or if the condition is difficult to control medically, a definitive treatment must be considered (8). The choice is between surgery and radiiodine. We prefer the latter because it is more convenient for the patient, does not require a hospital stay or anesthesia, and so forth. Besides, the goiter in question is generally quite small (8).

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**References**

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Amaia Valentín Solvas was born on 4 February 1989. She was involved in sports from a very early age: she is a judo practitioner since she was 8 and holds a blue belt; she's been involved in aerobics, rhythmic gymnastics and downhill skiing from the age of 4; she is a well-integrated member of a skiing competition club in La Molina, where she trains on Saturdays and Sundays for five hours each day. In September 2004 she was selected to represent Spain at the Special Winter Olympics held in Nagano, Japan, from 22 February to 6 March 2005. There were 1,800 athletes competing at these games. She placed fourth in the downhill and slalom events and won a gold medal in the special slalom event. She entered the Catalan Track and Field Championship organized by the Catalan Federation, and won a gold medal for her 100-metre sprint as well as a silver medal for her 3 kg shot put.