Thyroid disorders in subjects with Down syndrome: an update

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Summary. Down syndrome (DS) is the commonest chromosomal disorder among live born infants. DS is associated with increased risk of endocrine abnormalities particularly thyroid gland disorders. The spectrum of thyroid dysfunction in patients with DS include congenital hypothyroidism, subclinical hypothyroidism, acquired hypothyroidism (autoimmune - non autoimmune), and hyperthyroidism. This review will focus on the characteristics of the different presentations of thyroid abnormalities in DS, screening and management recommendations. (www.actabiomedica.it)

Key words: Down syndrome, hypothyroidism, subclinical hypothyroidism, autoimmune thyroid disorders

Introduction

Down syndrome (DS) is the commonest chromosomal disorder among live born infants. Its prevalence varies from 1 in 700 to 1 in 1500 live births (1). In 95 % of cases, Down syndrome is due to non - dysjunction of chromosome 21, while the remaining cases are either due to translocation or mosaicism (2-4).

DS is associated with increased risk of medical problems including gastrointestinal, cardiac, and pulmonary anomalies as well as developmental delay and endocrine abnormalities (5). Among the endocrine abnormalities, thyroid dysfunction is the commonest. It is estimated to occur in 4-8% of children with Down syndrome (6). The spectrum of thyroid dysfunction in patients with DS include congenital hypothyroidism, subclinical hypothyroidism, acquired hypothyroidism (autoimmune – non autoimmune), and hyperthyroidism (7).

Congenital hypothyroidism (CH)

Overt congenital hypothyroidism refers to elevated plasma TSH (>10 mIU/l) associated with low plasma T4 occurring at birth and in most cases diagnosed with neonatal screening (8). The prevalence of CH in DS is estimated to be 28-35 times higher than its prevalence in the general population (9). In the general population CH which is considered one of the most common preventable causes of mental retardation, is detected in 1 in 2000 to 3000 live births via neonatal screening.

The reported incidence of CH in Down syndrome is much higher, varying between 1: 113 and 1: 141 live births (10-12). Furthermore, the female preponderance observed in the general population with CH has not been found in patients with CH and DS (1).

The presence of CH increases the risk of the presence of other anomalies including congenital cardiac disease, respiratory distress syndrome, and gastrointestinal anomalies (13). The presence of CH in DS further increases the risk of congenital anomalies especially gastrointestinal and cardiovascular anomalies when compared to patients with DS without CH (5, 13-15).

A co-existence of CH and gastrointestinal anomalies is observed in DS. Jaruratanasirikul et al reported that Down syndrome babies with gastrointestinal anomalies at birth were "8.6 times more likely to have CH" (16).

Most cases of reported CH are due to thyroid hypoplasia (8, 17, 18). Other ultrasound findings included thyroid ectopia, athyreosis, or partial agenesis, but all are uncommon causes of CH (8, 9, 19). However, in most cases there is no abnormality on ultrasound scanning (17, 20-22).

Luton et al. studied the development of 13 human fetal DS thyroid glands between 23 and 33 weeks of gestation. They found that thyroid glands in DS were smaller in size and had fewer and smaller follicles compared to control thyroid glands. This was confirmed by immunohistological analysis with anti-NKX2 - 1 antibody. Fewer stained colloids were found upon antithyroglobulin staining. Furthermore, they found that TSH levels were above the 80th percentile in all foetuses and FT4 were below the 50th percentile in the majority. This supports the observation that thyroid hypoplasia is the commonest abnormality in DS patients with CH (23).

Few studies looked at the possible etiology of CH in patients with DS. Some hypotheses have been suggested including the following (1, 5):

1. Exaggerated response to TRH stimulation: delayed maturation of the hypothalamic - pituitary - thyroid axis leading to higher TSH levels with normal fT4 and fT3 levels and negative antithyroid antibodies in the first 3 years of life (24).
2. Peripheral resistance to thyroid hormones: leading to inappropriate TSH secretion. This was postulated to be due to abnormal thyroid hormone receptor function (24).
3. Inappropriate TSH release, due to a central disorder, or due to altered dopaminergic control resulting from reduction in dopamine production. Dopamine is an inhibitor of TSH (17, 24).
4. TSH insensitivity (5).
5. Reduced TSH bioactivity (5).

Subclinical hypothyroidism (SH)

SH refers to isolated elevation of TSH with normal thyroid hormone levels. Some authors refer to it as "mild hypothyroidism" (5), or "compensated hypothyroidism" or "isolated thyrotropinaemia" (10).

SH is probably the most common detected thyroid abnormality in these subjects (10). The incidence of SH varies in the literature depending mainly on the study size, and the TSH cut off for the definition of SH (1, 5, 10). Generally, TSH above 5 mIU/L is considered above the normal range in many places. Some studies refer to cases where TSH is less than 20 mIU/L as "compensated hypothyroidism" (5, 22). Others have defined two separate entities depending on whether TSH level is between 6 and 10 mIU/L or 11 and 20 mIU/L (5).

The questions that need to be answered regarding SH are many, among which are the exact definition of SH, the true incidence, its cause, whether it requires treatment or not, and at what TSH level should treatment be initiated, its natural course if left untreated, and whether treatment would have a positive impact on growth and neurodevelopment.

Elevated TSH above 5 mIU/L is widely accepted as elevated, and in the context of normal thyroid hormone levels, it is often referred to as subclinical hypothyroidism (7).

Among their 52 studied patients with SH, Pierce et al. reported that 30 patients had TSH between 5-10 μIU/mL, their mean TSH was 7.9 μIU/mL, and mean age at diagnosis was 5 years and 3 months, while 22 patients had TSH >10 μIU/mL, mean TSH level was 16.2 μIU/mL, and mean age at diagnosis was 5 years and 7 months (7).

The prevalence of SH in subjects with DS varies between 7 and 40% (1, 8, 21, 25-27). Figures between 25% and 30% have also been published (10, 22, 28). It is diagnosed irrespective of prematurity, low birth weight, or perinatal risk factors (8). In most cases, SH is asymptomatic, and is detected upon laboratory testing or neonatal screening (8, 26, 27). Some patients exhibit mild symptoms such as hypotonia or weight gain, but these symptoms often exist in patients with Down syndrome, and therefore would be difficult to rely on for diagnosis (8, 25, 29).

The cause of SH is unclear. Ultrasound scans showing goitre or thyroid hypoplasia were reported in newborns with SH (17, 21). Agenesis or ectopia is rarely reported, and in the majority of cases, normal thyroid gland is present (8). Autoimmunity is among the hypothesized causes of SH. Thyroid peroxidase (TPO) antibodies were detected in patients with SH

(10, 27, 30) and in some cases a self limiting autoimmune process was postulated (30).

In the study by Pierce et al., 37 patients out of 76 DS patients with SH were tested for thyroid antibodies. Positive antibodies were detected in 46% of the tested patients. 59% of their SH cohort had TSH level between 5-10 µIU/mL of which 25% had positive antibodies, and 35% had TSH >10 µIU/mL with positive antibodies in 66%. So the likelihood of antibody positivity was higher with higher TSH levels (7). Over expression of the gene of interferon receptor 1, which is located on chromosome 21, resulting in exaggerated response to interferon was recently suggested (10, 31, 32).

The natural course of SH is not consistent, and that is the reason debate often exists about whether or not to treat. Transient SH has been noted in several studies (10, 11, 30).

Gibson et al. studied 103 patients with DS for thyroid dysfunction. They found that 70% of those with elevated TSH normalized their TSH level 4-6 years later (30). Another study found that 27% of their DS patients (44 children) had SH, and 80 % of those retested for abnormal thyroid functions (8 out of 10) had normal TSH levels. No risk factor could be identified that favoured persistence of TSH elevation or progression to overt hypothyroidism (15).

Gibson et al. 2005 found that 8 of 17 patients with SH showed spontaneous resolution (30) . Claret al. suggested that SH in DS children less than 5 years of age is mostly transient in nature. Spontaneous resolution occurred in 73.6% of their 53 studied patients. They also stated that the presence of goitre or antithyroid antibodies is associated with lower remission rates (27). Overall, it is estimated that the incidence of progression of SH to overt hypothyroidism is less than 50% (25, 27, 30).

Treat or not to treat SH?

Because of the transient course observed in several studies, many authors are in favour of not treating SH (1, 4, 22, 27, 30, 33, 34). The rate of conversion to overt hypothyroidism has been reported to be low in a follow up study in adult patients with DS followed for 10-15 years (35).

The incidence of conversion of SH to overt hypothyroidism is estimated to be less than 50% (25, 27, 30). Furthermore, treatment does not seem to positively impact growth and development in treated compared non treated patients (4, 5, 22, 27, 30, 33, 34, 36). In the follow up of their randomized controlled trial, Marchal et al. found no difference in mental or motor development, weight, height, and head circumference between those treated with T4 and those given placebo, though treated patients were observed to be taller and with larger head circumference. This was not noted in patients with TSH level <5 mU/l. They concluded that early T4 treatment in DS did not seem to be of benefit to the motor or mental development though it may positively affect growth (37).

For all the aforementioned reasons, it was suggested that treatment of SH be reserved to patients who progress to overt hypothyroidism, and those with TSH > 10 µU/mL in the presence of goitre or positive thyroid auto antibodies (1). On the other side, some authors argue that early T4 treatment is potentially harmless, and may benefit growth and motor development in DS, a population with already delayed development (10, 28). Better intellectual outcome was also suggested with early treatment of mild cases (11). This was argued against by the work of Marchal et al and van Trotsenburg et al. (37, 38) Despite the detection of a minor benefit in growth and gross motor development with treatment during the first 2 years of life in their randomized controlled trial, the difference in motor and mental was insignificant when patients were reassessed after 8.7 years (37). Some authors also suggested that early treatment may prevent progression to severe hypothyroidism (39).

In summary, the uncertain positive impact of treatment on growth and development, the lack of clear evidence regarding the benefits of early thyroxine treatment, and the fact that elevated TSH is mild and transient in many cases are not in favour of treating patients with SH with a long life medication. Treatment of SH is only advised by most authors in case of conversion to overt hypothyroidism (1, 8). It can also be initiated in the presence of goitre, and some advocate treatment in the presence of positive thyroid antibodies as well provided TSH level is >10 µIU/mL (10).

Shifted TSH and T4 levels

Patients with Down syndrome are frequently observed to have TSH levels in the higher normal range, and T4 levels in the lower normal range (19, 40). van Trotesenberg et al. suggested that the mean plasma TSH and T4 levels in DS follow a Gaussian distribution with mean TSH shifted to right and mean T4 shifted to the left, and they considered this phenomenon as a continuum with SH (40). This may be a cause for over diagnosis of SH (7). Indeed, the data presented by Pierce et al agree with this hypothesis. The upper limit of normal TSH in their study was found to be 2.5 SD above the mean TSH value, which was 7.1 µIU/mL (7).

Autoimmune thyroid disorders

It is well known that autoimmune disorders are more common in DS patients compared to the general population (1). Among the autoimmune disorders reported celiac disease with a prevalence of 5-10%, type I diabetes mellitus which is claimed to be three times higher in DS patients (5), alopecia with recent reported rate of 11.4 % (41), and autoimmune thyroid disease (5, 10). Both hypothyroidism and hyperthyroidism are described in the literature, with autoimmune hypothyroidism or Hashimoto's thyroiditis (HT) being more common than hyperthyroidism or Graves' disease (GD) (1, 41). Thyroid auto antibodies are detected in 13-34% of patients with DS (5). Thyroid peroxidase (TPO) antibodies have been found in up to 31% of DS patients (36). In fact the presence of TPO antibodies strongly correlates with the evolution of euthyroidism and SH to overt hypothyroidism (10).

Hashimoto's thyroiditis and Graves' are recently considered as two sides of a coin (42). The commoner scenario has been conversion of GD to HT, whereas in patients with chromosomal abnormalities like Turner and DS, it was observed that the opposite scenario was more frequent (43).

Autoimmune hypothyroidism

The main features of autoimmune hypothyroidism in DS versus the general population are: 1) equal sex distribution, 2) earlier age of onset, 3) lower antibody titre at diagnosis, 4) lower rate of positive family history, 5) higher rate of progression to overt disease, 6) subclinical hypothyroidism being the most commonly observed picture on presentation, and 7) more common association with other autoimmune diseases (1, 5, 10, 41).

Autoimmune hypothyroidism in DS is equally common among both genders in contrast to the female preponderance observed in non DS population (1, 5, 10, 41). Another different point is the earlier detection of thyroid autoantibodies, though not necessarily associated with overt hypothyroidism.

Thyroid antibodies were detected in infants as young as 5 months of age (15, 44). Many authors stated that autoimmune hypothyroidism is usually diagnosed after the age of 8 years (5, 15, 39, 44). However, most of the published literature is limited by the small sample size. In their study on 146 patients with HT and DS compared to 553 patients with HT without DS.

Aversa et al. found that the mean initial age at diagnosis of HT in DS was 6.5 years compared to 11.1 years in non DS patients, 73.3% were younger than 10 years in the DS group whereas 32.5% were less than 10 years of age in the non DS group. They concluded that HT occurred at a younger age (41). It is hypothesized that this conclusion might be related to the increased awareness of the increased association of autoimmune disorders with DS among physicians, and therefore tendency to early testing of patients. Deterioration of the thyroid disease is the usual course of autoimmune thyroid dysfunction in DS. Almost all euthyroid patients studied by Aversa et al deteriorated to a state of hypothyroidism (41). The prevalence rate of SH remained constant in their cohort, while hyperthyroidism prevalence changed from 4.1% (6 patients) at initial evaluation to 8.2 % (12 patients) at re evaluation after a minimum period of 5 years. In fact, they quoted that "in 8.2% of cases HT switched to GD from presentation to re-evaluation". They emphasized that evolution of HT to hyperthyroidism is more frequent in DS (41).

Several studies tried to explain the increased incidence of autoimmune diseases in DS (1, 45, 46). Theories from different studies include the following:
- Thymic atrophy and reduction in T and B lymphocytes in the neonatal period. T lymphocytes

normalize with time but the B lymphocyto-penia persists. Reduced IgM, IgG2 and IgG4, with high levels of IgA, and IgG1 and IgG3 are observed. In addition, reduction in CD4+ cells associated with increased CD8+ lymphocytes all lead to altered immune function in DS, and increased incidence of autoimmune diseases and infections (1, 45, 46).

- Mutations in the autoimmune regulator gene (AIRE) located in the 21q22.3 region. AIRE is a transcription factor involved in immune regulation, and inactivate mutations in this gene are linked to polyendocrine syndrome type 1 (APS − 1). Although hypothyroidism is not a hallmark of APS − 1, it is observed in such patients. (47) The exact link between AIRE and autoimmune thyroid disease in DS has not been clearly established, yet over expression of this gene caused by the presence of an extra copy of chromosome 21 may be the explanation (48).

- Alterations in regulation of pro and anti inflammatory cytokines due to alterations in ATP and adenosine, nucleotides and nucleosides responsible for immune regulation (15).

- The suppressive effect of interferon alpha and its toxic effect on thyroid gland. Interferon alpha down regulates the expression of genes involved in T4 synthesis in vitro. Over responsiveness to interferon is hypothesized by few authors (5).

- An association with DQA1 0301 allele which is found on chromosome 6. This allele is linked to increased association of autoimmune thyroid disease and celiac disease. Up regulation of DQA1 0301 allele by immune regulatory genes located on chromosome 21 was suggested to be the cause behind increased prevalence of autoimmune thyroiditis in DS. (49) However no specific HLA genotype has been proved to be related to thyroid autoimmunity in DS (5, 49).

Regarding the treatment of hypothyroidism, overt hypothyroidism manifested as elevated TSH combined with low free T4 requires thyroid hormone replacement. The presence of positive antithyroid antibodies in the absence of biochemical evidence and clinical symptoms does not warrant treatment but needs careful and strict follow up and more frequent biochemical testing to detect overt changes in thyroid functions (1). SH is still a debatable matter as was discussed earlier.

Autoimmune hyperthyroidism

Graves' disease is the main cause of hyperthyroidism in DS (50, 51). It is observed more frequently in DS, but without sex predilection compared to the general population (50). Its prevalence is estimated to be 0.66% compared to 0.02% in the general population (51).

Contrary to autoimmune hypothyroidism, Graves' disease in DS is usually symptomatic and easy to discover (50, 51). It commonly presents in late childhood or early adult life (5), but is generally earlier to present when compared to the general population. It is also commonly associated with other autoimmune disorders (1), and is commonly a result of progression from HT regardless of the degree of autoimmunity at presentation (43, 52).

In their follow up series of 12 DS patients initially diagnosed with HT and converted to GD over a median period of 4.2 years (9/12 were either euthyroid, SH, or overt hypothyroid, and all 12/12 had negative TRAB at initial diagnosis), Aversa et al. found that the time to conversion from HT to GD was not related to L-thyroxine treatment, and that serum TRAB concentrations did not differ between those treated with L-thyroxine and those not treated. All their patients showed long and persistent remission after an initial methimazole dose of 0.38±0.12 mg/kg/day. After a median period of 2.5 years (range 2-7 years), 8/12 patients are still being treated with a mean dose of 0.12±0.02 mg/kg/day to maintain euthyroidism (53).

From our experience, this is a reasonable dose. Hypothyroidism may develop after withdrawal of methimazole treatment and require L-thyroxine treatment (42, 53, 54). The main challenge is the treatment modality. Shorter duration of remission (50), and higher relapse rates are observed with medical treatment (5). Relapse rate after withdrawal of medication varies but rates up to 100 % have been published (50, 51). For this reason, it is suggested that treatment with radioactive iodine may be the best option (50, 51).

Several reports have been published in favour of radio-active iodine treatment in DS. However, this necessitates life - long L thyroxine replacement (51, 55).

On the contrary, De Luca et al. reported that Graves' disease in DS has less severe clinical course compared with patients without DS, they also found lower relapse rate after withdrawal of methimazole first cycle, and the persistence of remission was higher in DS after withdrawal of definitive treatment. However, their population consisted of only 28 DS patients compared with 109 controls (50). In the paediatric population, it may be difficult to use radioactive iodine as a first choice for treatment. Surgery is reported not to be the best choice in patients with DS because of the craniofacial abnormalities and the short neck that may interfere with anaesthesia (1, 5). Every treatment modality has its pros and cons and no single treatment can be generalised in all patients.

Screening recommendations

According to the American Academy of Paediatrics, it is suggested to check TSH at birth, 6 and 12 months then annually thereafter (56). The Australian and Canadian guidelines recommend the same (57, 58). In their study, Erlichman et al. emphasized the importance of TSH based screening. They concluded the total T4 based neonatal screening failed to identify many cases of congenital hypothyroidism in neonates (59). If TSH is abnormal, or there is clinical suspicion, free T4 is to be checked as well (59). For patients with SH, there are different suggestions including routine screening (15), screening every 5 years (30), and every 3 months (22).We believe that more frequent testing should be performed in patients with SH.

Regarding thyroid antibody testing, only the Irish and the UK guidelines referred to thyroid antibody measurement with each thyroid screen, which they recommended to be at least once every two years starting from age 1 throughout life (60, 61). It could be argued that patients with positive antibodies are more likely to progress to overt hypothyroidism, and therefore antibody testing can be a useful tool to anticipate progression to overt hypothyroidism (10). This would justify more frequent testing.

Conclusion

More understanding of the mechanisms behind thyroid gland dysfunction in DS has evolved over the recent years. There seems to be peculiarities regarding the presentation of autoimmune thyroid disease in DS. The metamorphism of thyroid autoimmunity in DS is common, and warrants careful follow up. The "watchful waiting" strategy is generally becoming more popular for subclinical hypothyroidism, with more frequent testing warranted for this subgroup that represents the majority. There is more evidence regarding the value of radioactive iodine treatment for Graves' disease. Up till now, there is no uniformly worldwide accepted consensus regarding the frequency of screening after the first year of life, and regarding the TSH cut off value for starting treatment.

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