

# **Thyroid dysfunction in Down's syndrome: A review**

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**Clinical forms of hypothyroidism found in individuals with Down's syndrome include transient and primary hypothyroidism, pituitary-hypothalamic hypo-thyroidism, thyroxin-binding globulin (TBG) deficiency and chronic lymphocytic thyroiditis. Hyperthyroidism also occurs occasionally. The frequency of thyroid disease is elevated in patients with Down's syndrome, starting in the newborn population where it is 0.7% (or 28 times more frequent than in the general population). Twelve per cent or more of adults with Down's syndrome have thyroid disease. Thyroid disease is difficult to diagnose clinically in individuals with Down's syndrome because of an overlap of symptoms. This makes thyroid blood screening a particularly important part of the annual preventive medicine screening of each person with Down's syndrome.**

In 1866, John Langdon Down made his great contribution by differentiating children with cretinism (neonatal hypothyroidism) from children with Down's syndrome (Down 1866). The clinical resemblance between the two patient groups makes it very difficult to this very day for a physician to detect developing thyroid disease in a child with Down's syndrome (Abassi 1980). See Table 1 on page 130.

Yet, although it is very difficult to detect just by physical examination, it is most important that the clinician pick up developing thyroid disease in children and adults with Down's syndrome. Hypothyroidism can affect a child with Down's syndrome at any age as was shown in a study where none of the cases had yet presented with clinical signs; the hypothyroidism already present in the children being picked up by routine TSH screening as part of an annual preventive medical screen (Abassi and Coleman 1984). It is very easy to treat; yet if left untreated, hypothyroidism limits both intellectual and physical development of the child. Thus the annual preventive medical protocols for individuals with Down's syndrome of all ages always should include a blood test for thyroid disease, usually TSH (Rogers and Coleman 1992).

How likely are individuals with Down's syndrome to have a problem with thyroid function? The studies suggest that the percentage of individuals with Down's syndrome at risk for thyroid disease gradually increases with age. At birth, 0.7% of the infants with Down's syndrome have persistent primary congenital hypothyroidism (Fort et al. 1984) whereas the figure for adults with hypothyroidism rises to at least 12% (Korsager et al. 1978).

## **Newborn studies**

The routine screening for congenital hypothyroidism in every newborn that exists in many countries has removed the difficulties of diagnosis in the neonatal period (Fisher et al. 1979). Occasionally athyreosis has been described in infants with Down's syndrome but it is relatively rare (Verma and Ghai 1971; Zergollern et al. 1974; Hook 1980). However, in one of the largest newborn studies ever done, the incidence of persistent primary congenital hypothyroidism of all types in infants with Down's syndrome was 1:141 compared to 1:3800 in the general population; this is an incidence 28 times more frequent in Down's syndrome (Fort et al. 1984). Cutler et al. studied 49 children less than three years of age and found that three had congenital hypothyroidism (Cutler et al. 1986). He noted that 27% of them already had mildly increased TSH levels. There are studies from many countries that have documented hypothyroidism in young infants with Down's syndrome (Verma and Ghai 1971; Zergollern et al. 1974; King et al. 1978). In some patients, however, the neonatal hypothyroidism is transient and follow-up is always needed (Fort et al. 1984; Colombo et al. 1992).

Exactly why the incidence of hypothyroidism is elevated in neonates with Down's syndrome is not fully understood. One group of investigators found that there is an increased incidence of maternal thyroid disease in mothers of newborns with Down's syndrome (Fialkow et al. 1965; Dallaire and Flynn 1967; Vanhaelst et al. 1970; Fialkow et al. 1971). However, recent studies have found no increase in the prevalence of thyroid antibodies in mothers of infants with Down's syndrome compared to controls (summarised in Torfs et al. 1990).

Characteristic	Down's Syndrome	Hypothyroidism
Appearance	Dull, chubby	Dull, chubby
Head	Microcephalic	Normal
Tongue	Large	Large
Nasal bridge	Underdeveloped	Underdeveloped
Eyes	Slanted	Not slanted
Neck	Short	Short
Heart	Murmur (AV canal)	Murmur (thick valve and septum)
Abdomen	Protuberant umbilical hernia	Protuberant umbilical hernia
Neuromuscular	Hypotonia	Hypotonia
Skin	Dry	Dry
Extremities	Short, transverse palmar crease	Short, no transverse
Development	Retarded	Variable

Table 1. Comparison of Physical Characteristics of Children with Down's Syndrome and Hypothyroidism.

It has been noted that maternal serum in pregnancies with a Down's syndrome foetus have increased concentration of human chorionic gonadotrophin (hCG) and low concentrations of both alpha-foetoprotein and unconjugated oestriol; in fact these tests are widely used in prenatal screening (Wald et al. 1988; Petrocik et al. 1989). Although they may simply be markers for an immature foetal-placental unit, it is also possible that they may play a direct role in the pathogenesis of autoimmune thyroid disease (Kennedy et al. 1992). Human chorionic gonadotrophin is structurally similar to pituitary thyrotrophin (TSH) and may play a part in thyroid regulation during normal pregnancy; hCG can bind to thyroid cells and modulate their function (Kennedy and Darne 1991). High concentrations of hCG, which can have antagonist as well as agonist actions on the thyroid, may contribute to maternal and foetal thyroid abnormalities while hyperstimulation of the thyroid in some pregnancies might increase presentation of autoantigen to the immune system.

### Childhood studies

During childhood, the problem of diagnosis of hypothyroidism by clinical criteria alone remains a difficult one. The importance of annual preventative medical blood testing can not be overstated (Rogers and Coleman 1992). Goitre, which can be seen with hypothyroidism, hyperthyroidism or even euthyroidism is one the more obvious clinical clues (Hayle et al 1965). By the time that the prominent features of severe hypothyroidism (growth deviation from a previous channel of growth, plateauing of intellectual growth, increased lethargy, constipation and eventually the development of myxedema) are seen in the patient, the child with Down's syndrome is already having major adverse effects of the disease process. Very rarely there is an unusual presentation of hypothyroidism in young people with Down's syndrome such as vaginal bleeding (Hubble 1963; Lund 1959) or cardiac tamponade (Heydarian and Kelly 1987).

In 1985, Pueschel and Pezzullo reported on the results of 151 children with Down's syndrome and their sibling controls. The children with Down's syndrome were three to 21 years old. In this series, 27% had an abnormality of TSH,  $T_4$  or both. They noted that there were higher TSH concentrations in adolescents and decreasing  $T_4$  levels with the advancing age of the patients. These authors even raised the question of whether the decline of intelligence quotients described in the literature over time in persons with Down's syndrome might be, in part, due to undetected, inadequate thyroid function (Pueschel and Pezzullo 1985). A 1993

study of children with Down's syndrome looked at one aspect of that problem - whether the elevation of TSH in the presence of normal levels of  $T_4$  and  $T_3$  affected growth or intellectual performance - and found no difference between children with and without elevated TSH (Selikowitz, 1993).

Loudon et al. also published a series in 1985 of 116 home-based children (Loudon et al 1985). Three were hypothyroid and one was hyperthyroid but they found thyroid antibodies in 29% of the children and also a high incidence in the normal relatives and controls used. The authors noted that transient increases in TSH levels seemed common in these children, particularly during periods of intercurrent illness. In 1990, Van Dyke et al. evaluated 132 children from two months of age to 19 years of age and found that 8% had some abnormality of thyroid function (Van Dyke et al. 1990).

In 1991, Pueschel updated his series to 181 patients and found 6% of children had both high TSH and low  $T_4$  (Pueschel et al. 1991). An Italian series with a mean age of six years and five months found 3.6% of the children were hypothyroid (Colombo et al 1992). In 1993, a five year longitudinal study was published of 101 children with a mean age of five years and three months (Selikowitz 1993). During the course of the study, in addition to the three children who entered the study with abnormal thyroid tests, eight more children developed elevated TSHs, in all cases with otherwise normal  $T_4$  and  $T_3$  tests. Only one of these eight then further developed uncompensated hypothyroidism; this patient had thyroglobulin and microsomal thyroid antibodies.

Autoimmune thyroid disease generally is very uncommon in young children but has been recognised in association with Down's syndrome (Harris and Kontsoulieris 1967). The pathogenesis of autoimmune thyroid disease is complex and, to date, there is no single unifying hypothesis to account for the changes in immune function and the increased incidence of autoimmune thyroid disease in patients with Down's syndrome. There is an interest in the possible effects of over expression of proteins whose genes are encoded on chromosome 21 and which participate in the regulation of the immune response (Kennedy et al 1992). Increased expression of chromosome 21 gene products may be directly responsible for altered immune function and predisposition to autoimmune disease. The interferons (IFNs) and lymphocyte function-associated antigen-1 (LFA-1) are of particular interest in this research.

## Adult studies

The older the patient with Down's syndrome is, the more likely is the development of thyroid dysfunction (Murdoch et al 1977). In a 1990 study of 106 adults from 20 to 67 years of age (with an average age of 38 years), 40% had test results of abnormal thyroid function. However, it should be noted that not all patients with abnormal test results had an active disease process: only seven had active hypothyroidism and one had thyrotoxicosis (Dinani and Carpenter 1990). Clinical forms of hypothyroidism found in persons with Down's syndrome include transient and primary hypothyroidism, pituitary-hypothalamic hypothyroidism, thyroxine-binding globulin (TBG) deficiency and chronic lymphocytic thyroiditis.

A major unsolved problem regarding hypothyroid studies in patients with Down's syndrome is the question of why so many individuals have elevated TSH levels in the presence of normal thyroid hormone ( $T_4$ ) levels. Such patients are found in many of the series discussed above. A first step of understanding this problem is the finding of exaggerated TSH responses to thyrotropin-releasing hormone recorded in these individuals who have elevated levels of TSH yet normal levels of  $T_4$  (Pozzan et al. 1990).

## Hyperthyroidism

Hyperthyroidism also occurs in Down's syndrome. In series reporting on the frequency of hypothyroidism in Down's syndrome, one or more cases of hyperthyroidism may be mentioned (Cutler et al. 1986; Loudon et al. 1985). Exophthalmus is even rarer. In children with Down's syndrome, clinical recognition of hyperthyroidism can be difficult because symptoms may be masked. Suggestive findings of hyperthyroidism include weight loss, hyperactivity, diarrhoea, nervousness and goitre. However, the shortness and chubbiness of the neck makes it more difficult to detect thyromegaly so careful palpation is necessary.

## Conclusion

Thyroid disease occurs with greater frequency in individuals with Down's syndrome than in control populations. Patients are at risk from infancy through adult life. The effect of the onset of hypothyroidism in a child with Down's syndrome can be devastating - plateauing or even loss of intellectual function achieved after so much work with infant learning programmes, sluggishness, constipation and growth deviation from a previous channel of growth. All this can be prevented by thyroid blood test which is part of an annual preventative medical screening for each individual with Down's syndrome. Interpretation of thyroid test results always should be made by a specialist who is aware that elevated TSH levels sometimes are transient in Down's syndrome.

## Glossary

**Alpha-fetoprotein (afp):** A protein formed in the liver of the foetus and present in the amniotic fluid in small amounts. The amount present is increased in spina bifida and decreased in Down's syndrome.

**Athyreosis:** Absence of or lack of function of the thyroid gland.

**Cardiac tamponade:** Abnormal pressure on the heart caused by the presence of excessive fluid between the pericardium and the heart.

**Euthyroidism:** Having a normally functioning thyroid gland.

**Exophthalmus:** Protusion of the eyeballs in their sockets. Sometimes associated with overactivity of the thyroid gland.

**Goitre:** Swelling of the neck due to enlargement of the thyroid gland.

**Human chorionic gonadotrophin (HCG):** A hormone, similar to the pituitary gonadotrophins, produced by the placenta during pregnancy.

**Hyperthyroidism:** Overactivity of the thyroid gland.

**Hypothyroidism:** Subnormal activity of the thyroid gland.

**Hypothalamus:** The region of the forebrain which has many functions and acts as a centre for the integration of hormonal actions.

**Interferons (IFNs):** Substance that is produced by cells infected with a virus and has the ability to inhibit growth.

**Microsome:** Intracellular particle consisting of part of the endoplasmic reticulum and microsomes. microsomal thyroid antibodies

**Myxoedema:** The clinical syndrome due to hypothyroidism.

**Thyrotrophin (TSH):** The hormone that stimulates activity of the thyroid gland.

**Thyromegaly:** Enlarged thyroid gland.

**Thyrotoxicosis:** The syndrome due to excessive amounts of thyroid hormones in the bloodstream.

**Thyroxine-binding globulin:** The blood protein to which thyroxine is attached.

**Unconjugated oestriol:** One of the female sex hormones.

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## **Thyroid Disorder: Current advice to medical practitioners in the U.K.**

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1. Thyroid disorder (usually hypothyroidism) is commoner in people with Down's syndrome than in the general population. This is true at all ages but it becomes more common with age (approx. 35% in adults).
2. If we relied on making the diagnosis on clinical grounds alone many cases would be missed.
3. Treatment is usually beneficial.
4. Within the population of people with Down's syndrome, hypothyroidism does meet most of the WHO criteria for

a screening programme. We therefore feel that screening for hypothyroidism is desirable.

5. All babies in the U.K. have a neonatal screen for hypothyroidism. For children with Down's syndrome each district should have a policy for screening after this, starting in infancy and continuing throughout life.
6. Screening should occur at least once every three years, and probably more frequently in adulthood (1-2 yearly).
7. The screening test should include estimation of T4, TSH and thyroid autoantibodies. Raised TSH, or the presence of antibodies with normal T4 and no clinical evidence of hypothyroidism does not warrant treatment but may indicate increased likelihood of developing clinical hypothyroidism. These children should therefore be tested more frequently, i.e. annually.
8. Clinicians should always bear in mind the prevalence of thyroid disorder in people with Down's syndrome and have a low threshold for testing thyroid function if there is any clinical suspicion at times between the screening tests.