

Hypothyroidism Due to Auto-immune Thyroiditis in a Young Child with Down's Syndrome

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Evidence suggesting an increased incidence of thyroid disorders in patients with Down's syndrome is accumulating (Mellon, Pay, and Green, 1963; Burgio, Severi, Rossoni, and Vaccaro, 1965; Fialkow, Uchida, Hecht, and Motulsky, 1965). In this paper we report the association of trisomy 21, with severe acquired hypothyroidism due to auto-immune thyroiditis in a girl of 3½ years.

Case Report

An infant girl was diagnosed at birth as having Down's syndrome. Cytogenetic studies demonstrated a normal karyotype in the mother and trisomy 21 in the patient (Dr. E. Blank).

In February 1963 the patient, aged 9 months, was admitted to the Children's Hospital, Sheffield, with acute laryngo-tracheo-bronchitis. At this time she was noted to have typical features of Down's syndrome (Fig. 1). Her course in hospital was uneventful and she was discharged after 7 days.

She was readmitted in March 1966 at the age of 3 years and 10 months. On this occasion the presenting symptoms were pallor and constipation. The parents

noted that from the age of 2 years there was coarsening of the facial features (Fig. 2) and increasing sluggishness in her behaviour. She could walk with support at 15 months, but had progressed no further, and shortly before admission had become unable to walk even with support. In the three months before admission yellow areas of discoloration in the wrist creases and on the knees and elbows had become marked, and constipation had become very severe.

Family history. The mother had had three pregnancies. The first terminated spontaneously at 28 weeks with delivery of a male infant with multiple congenital abnormalities, who survived for one hour. The propositus is the product of the second pregnancy when the maternal and paternal ages were 27 years. The third pregnancy terminated spontaneously with the birth of a normal full-term male infant.

Examination. The patient was lethargic, underweight (10 kg.), and dwarfed (74 cm.). Her facial features were of both Down's syndrome and severe hypothyroidism (Fig. 3). The thyroid gland was not palpable. There was bright yellow staining in the creases on the palmar aspect of the wrists and similar patches of discoloration on the knees. The left second toe was conspicuously

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FIG. 1.—Patient, age 1 year.



FIG. 2.—Patient, age 2 years 3 months.

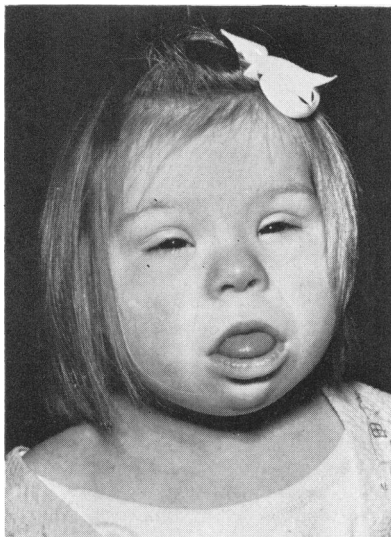


FIG. 3.—Patient, age 3 years 10 months.

enlarged and yellow. The pulse rate was 80 per minute. The heart and lungs were normal. The liver was enlarged to 2.5 cm. below the costal margin and was firm. All the reflexes were present but not brisk. She was unable to stand unsupported and did not attempt to crawl. When placed prone she would lift her head for a short while and then lie completely flat. Her favourite position was to sit upright and rock to and fro.

Investigations. Urinalysis was within normal limits. Hb 9.7 g./100 ml.; ESR 50 mm./hr.; total serum lipids 2.5 g./100 ml.; cholesterol 1250 mg./100 ml.; protein bound iodine 2.5 μ g./100 ml.; creatine phosphokinase 7.3 μ mole/ml. hr.; alkaline phosphatase 4 King units; sodium 134 mEq/l.; potassium 4.9 mEq/l., and bicarbonate 19 mEq/l.; urea 31 mg./100 ml.; total protein 6.6 g./100 ml. Electrophoresis of plasma showed moderate increase in α_2 and γ -globulin. Urinary 17-hydroxycorticosteroids 0.08 mg./24 hr., and 17-ketosteroids 0.05 mg./24 hr.; urinary oestriol 8 μ g./24 hr., oestrone 2 μ g./24 hr., and oestradiol 2 μ g./24 hr.

Pituitary gonadotrophins were < 0.4 i.u./day. Plasma thyrotrophic hormone was clearly detectable by the McKenzie bio-assay method in keeping with the usual experience in adult primary myxoedema (Dr. D. Monro). Thyroid antibodies: thyroglobulin tanned cell agglutination titre 1/10; colloid antibodies immunofluorescent positive; cytoplasmic antibodies immunofluorescent positive; cytoplasmic antibodies complement-fixation titre 1/256; no gastric parietal cell or non-organ-specific auto-antibodies were found.

Serum from the mother and sib was negative for thyroid and gastric auto-antibodies (Dr. D. Doniach).

X-ray examination of the wrist showed a bone age of 2 years (CA 3 10/12 years); and of the pelvis revealed

shallow acetabula and iliac angles; no epiphysial dysgenesis was seen.

The electrocardiogram was normal.

Treatment was started with L-thyroxine in a dose of 25 μ g. daily and increased to 0.1 mg. daily. After 10 weeks of treatment the creatine kinase was 2.1 μ mole/ml. hr., alkaline phosphatase 16 King units, cholesterol 163 mg./100 ml., and protein bound iodine 10.7 μ g./100 ml. She became more alert within a few days of starting treatment, and within four months was able to walk without support and say single words with meaning. The facial features are now quite clearly those of Down's syndrome (Fig. 4).

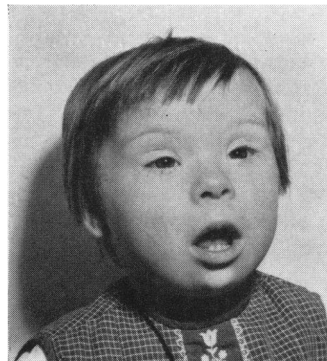


FIG. 4.—Patient, age 4 years 2 months.

Discussion

The patient described in this paper had trisomy 21 and gross acquired hypothyroidism. The finding of high titres of thyroid auto-antibodies was considered diagnostic of severe auto-immune thyroid disease. The coincidence of these two conditions in a patient of this age has to the best of our knowledge not been previously described. Mellon *et al.* (1963) reported a 29-year-old patient with Down's syndrome and myxoedema due to auto-immune thyroiditis. In their investigation into the occurrence of thyroid auto-antibodies among other patients with Down's syndrome, they found that 7 out of 35 patients (20%) had thyroid auto-antibodies in their serum, but only one had clinical thyroid disease. None of the 35 patients in the control group, matched for age, sex, and intelligence, had thyroid auto-antibodies detectable.

Burgio *et al.* (1965) were able to demonstrate a positive test for thyroid auto-antibodies in 7 out of 12 children with Down's syndrome and in 6 of the mothers, while in the group of 48 controls, among whom were 18 children and their mothers, they found 3 sero-positive children and 5 sero-positive mothers.

Similarly, Fialkow *et al.* (1965) found a strikingly

higher incidence of sero-positive results in 29% of a group of mothers with an affected child, but in only 9% of other mothers in the child-bearing age. No increased frequency of sero-positive fathers was found. It is unlikely that the association of auto-immune thyroiditis and Down's syndrome in the propositus is coincidental.

In spite of the above finding, the presence of hypothyroidism due to auto-immune thyroiditis in young patients with Down's syndrome appears to be a rarity. Isolated case reports of hypothyroidism in Down's syndrome have been published (Talbot, Sobel, McArthur, and Crawford, 1952; Esen and Mautner, 1957; Lunde, 1959; Hubble, 1963; Hayles, Hinrichs, and Tauxe, 1965). No information about thyroid antibodies is mentioned in these reports. In this connexion it is of interest that in the patient documented by Hayles *et al.* (1965), the erythrocyte sedimentation rate was raised (56 mm./hr.).

The patients reported by Lunde (1959), Hubble (1963), and Hayles *et al.* (1965) had primary hypothyroidism and exhibited precocious menstruation. This has been ascribed in part to hormonal overlap in the pituitary feedback mechanism (Van Wyk and Grumbach, 1960). Although our patient had a grossly raised thyroid stimulating hormone, no clinical evidence of sexual precocity was found, and the follicular stimulating hormone level in the urine was less than 0.4 i.u./day, but the level of urinary oestriol was considerably raised for her age (Eberlein, Bongiovanni, and Francis, 1958).

There have been fairly numerous studies of thyroid function in patients with Down's syndrome who were clinically euthyroid. The protein-bound iodine has invariably been within the normal range (Cottino, Ferraris, and Coda, 1956; McGirr and Murray, 1956; Bellack and Albaum, 1957). Investigations using radioactive iodine have generally given similar results. The ¹³¹I uptake at 24 hours was found to be normal in a study of 50 patients with Down's syndrome and 68 euthyroid patients with mental retardation of various causes (Friedman, 1955). No six-hour uptake recordings were done and many of the patients with Down's syndrome had previously been on thyroid therapy which had been stopped 14 days before the test.

Kurland, Fishman, Hamolsky, and Freedberg (1957) obtained normal values for the 24-hour uptake in 21 patients with Down's syndrome, but the turnover rate of ¹³¹I by the thyroid was significantly faster than in the euthyroid group and the *in vitro* erythrocyte uptake of ¹³¹I-labelled triiodothyronine was raised. The significance of the increased rate of ¹³¹I turnover is uncertain, but the

explanation may lie in the presence of localized areas of hyperplasia in the thyroid gland found by Benda (1946) in 20% of his subjects. Whether they are in turn related to the presence of thyroid auto-antibodies is unknown and worth further study.

Gonadal dysgenesis is a further example of an aneuploid state in which Hashimoto's disease (Spakes and Motulsky, 1963) and thyroid auto-antibodies have been found (Williams, Engel, and Forbes, 1964). The altered thyroid function in Klinefelter's syndrome (Barr, Shaver, Carr, and Plunkett, 1960; Carr, Barr, Plunkett, Grumbach, Morishima, and Chu, 1961; Davis, Canfield, Herman, and Goler, 1963) does not appear to be related to an auto-immune mechanism. Day and Wright (1964) were unable to demonstrate significantly high titres in 16 patients with abnormalities of the sex chromosome complement of the Klinefelter variety; nor were they present in parents of patients with chromatin positive Klinefelter's syndrome (Ferguson-Smith, Anderson, Frøland, and Gray, 1966).

Fialkow (1964) suggested three possible explanations for the association between aneuploid conditions and thyroid auto-antibodies. First, the chromosomal aberration may predispose to the development of auto-antibodies in the patients. The demonstration of auto-antibodies in the sera of phenotypically normal relatives does not favour this suggestion, but extensive cytogenetic studies of sero-positive mothers have not been reported. Secondly, the presence of immunological aberrations in the parent may predispose to aneuploidy. Thirdly, a common factor may be responsible for both the immunological aberrations and the aneuploidy. The limited family study in this patient revealed a normal karyotype in the mother and no gastric or thyroid auto-antibodies were demonstrated in her serum or that of the younger sib.

The subject of thyroiditis in childhood has recently been reviewed by Leboeuf and Ducharme (1966). It is apparent that the true incidence of thyroiditis in childhood is unknown, but surveys in Boston (Saxena and Crawford, 1962), Philadelphia (Leboeuf and Bongiovanni, 1964), and Gothenburg (Nilsson and Doniach, 1964) have shown that thyroiditis is responsible for approximately 50% of goitres in euthyroid children. By 1965 only 158 cases of thyroiditis had been reported in the English and French reports, while 500 cases of thyroid carcinoma had been described by 1961 (Leboeuf and Ducharme, 1966).

It is likely that a greater awareness of the part played by thyroiditis in disorders of childhood

thyroid function would lead to the diagnosis being made more often.

Summary

A young child with trisomy 21 and acquired hypothyroidism due to auto-immune thyroiditis is described. Limited family studies were negative for chromosomal and immunological abnormalities. Thyroid function tests have generally been normal in Down's syndrome, despite an increased incidence of thyroid auto-antibodies. The pathogenesis of auto-immune thyroiditis and the presence of thyroid auto-antibodies in Down's syndrome is at present unknown.

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