abnormal ears, and flexion deformity of the left wrist and of the fingers.

Discussion

Recently, a case similar to ours has been described¹ in which an ultrasound examination at 17 weeks' gestation showed a fetus with a grossly distended urinary bladder owing to an atretic urethra. This pregnancy was terminated and later the fetal karyotype was found to be trisomy 18 (47,XY,+18). The amniotic fluid AFP was normal, whereas in our case the amniotic fluid AFP was markedly raised. Raised amniotic fluid AFP levels, however, are not exclusively found in open neural tube defects, but have also been reported with several other fetal abnormalities,² such as congenital nephrosis, Meckel's syndrome, Turner's syndrome (cystic hygroma), gastrointestinal atresias, trisomy 13, and omphalocele/exomphalos. Nevin *et al*³ described a case at 27 weeks' gestation with a large distended bladder secondary to urethral atresia, other congenital abnormalities, and a raised amniotic fluid AFP. The raised amniotic fluid AFP in omphalocele/exomphalos and in distended fetal bladder owing to absence of the urethra is presumably the result of transudation of fetal serum through the markedly thinned fetal abdominal wall. The present case showed a second band of specific AChE characteristic of an open neural tube defect. A raised AFP and specific isoenzyme for AChE has been reported in a fetus at 17 weeks with a large exomphalos (part of Edwards's syndrome).⁴ The two bands in gel electrophoresis were very similar to those in NTDs. The UK Collaborative Acetylcholinesterase Study⁵ reported a positive gel AChE result in 47 of 63 (75%) pregnancies with a raised amniotic AFP which resulted in exomphalos.

On ultrasonic examination at 19 weeks' gestation there was marked variation of fetal heart rate and at necropsy the fetus had severe congenital heart anomalies. The gross ascites may have resulted from fetal heart failure. Although renal malformations are frequent in trisomy 18,⁶ absence or atresia of the urethra is rare. Our case is the third to describe the antenatal recognition of absence of the urethra in association with trisomy 18.^{1 4}

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Graves' disease and Down's syndrome

SUMMARY A case is described of severe thyrotoxicosis occurring in a patient with Down's syndrome, in which behavioural disturbance was a marked but reversible phenomenon. In addition, we report that antibodies capable of stimulating the thyroid were detectable in the sputum of both the patient and his mother.

Autoimmune disturbances including diabetes, adrenal failure, chronic active hepatitis, and particularly hypothyroidism are common in Down's syndrome.¹ However, few previous cases of hyperthyroidism have been described in such patients,^{2 3} and although on clinical grounds the majority of these patients probably had Graves' disease, the presence of immunoglobulins capable of stimulating the thyroid (TSI) has not previously been reported.

Case report

A 35-year-old man with Down's syndrome presented in April 1982 with a one-month history of weight loss, sweating, diarrhoea, heat intolerance, and difficulty in climbing stairs. In addition he had become increasingly irritable, withdrawn, and difficult to manage and had developed visual hallucinations. There was no significant past medical history and no family history of autoimmune disease.

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Clinical examination revealed the features of severe thyrotoxicosis together with those of Down's syndrome. A smooth firm enlargement of the right lobe of the thyroid was detectable, but there was no evidence of Graves ophthalmopathy. His pulse was 130 per minute but there were no abnormal findings in the cardiovascular, respiratory, alimentary, or central nervous systems apart from mild proximal muscle weakness.

Investigations showed haemoglobin 15.2 g/dl, MCV 86 fl, urea and electrolytes normal, and serum creatinine normal. Serum thyroxine was 405 nmol/l (normal range 60 to 140) and serum triiodothyronine was greater than 10 nmol/l (normal range 1.2 to 3.0). Basal serum thyroid stimulating hormone levels were undetectable with no response to exogenous TRH administration. Thyroid cytoplasmic and microsomal antibodies were detectable and thyroid stimulating immunoglobulins⁴ were strongly positive(+++). Thyroid scan showed a very high uptake of ¹³¹I (81% at 6 hours). Distribution of isotope was a little patchy with greater uptake in the right lobe. Chest x-ray was normal and ECG showed sinus tachycardia only. Chromosome analysis confirmed trisomy 21. HLA typing showed A1, B8, B17, DR5, DR7. Investigation of his mother showed normal serum thyroxine and triiodothyronine and a normal TSH response to TRH. Autoantibodies were negative but thyroid stimulating immunoglobulins were present in low titre (+).

He was started on carbimazole 15 mg four times daily supervised by his mother. However, severe thyrotoxicosis persisted with profound weight loss over the next 2 weeks necessitating admission to hospital and treatment as for thyroid storm with carbimazole, propranolol, and potassium iodide. His symptoms abated, although raised thyroid hormone concentrations in the blood were detectable over the next 3 months despite carbimazole 45 ng daily, and he remained clinically mildly thyrotoxic. Visual hallucinations continued. Radioiodine (15 mCi) was therefore administered and euthyroidism was eventually achieved 5 months after presentation, by which time his behavioural disturbances had also resolved.

Discussion

The mechanism(s) of production of immune disturbance in Down's syndrome is uncertain and probably multifactorial,^{5,6} being further complicated in those who possess the allele HLA-B8.⁷

Although our patient was male the preponderance of Down's syndrome patients with thyrotoxicosis are female (16 F : 2 M), reflecting the incidence in the general population, while Down's syndrome occurs equally in both sexes.

Thyrotoxicosis in our patient was particularly severe and the demonstration of TSI confirmed the cause as Graves' disease. Thyrotoxicosis of this severity has been described only once before.²

Antibodies directed against thyroid tissue components are detected more often than expected in maternal relatives of children with Down's syndrome.⁸ These were absent in the mother of the index case. She did, however, have circulating immunoglobulins capable of stimulating thyroid tissue despite clinical and biochemical euthyroidism. Detectable thyroid stimulating immunoglobulins have not previously been described in maternal relatives of subjects with Down's syndrome.

Behavioural disturbance was an early and prominent symptom which responded only very slowly to antithyroid therapy. As hypothyroidism is also very common in adults with Down's syndrome it is suggested that thyroid function be carefully evaluated in such patients, particularly those in whom change in behaviour patterns occurs.

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that in Fabry's disease bouts of shooting pain can be caused by damage to dorsal root ganglia neurones.

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Correction

In the paper 'Graves' disease and Down's syndrome' by McCulloch *et al* which was published in *Journal of Medical Genetics* 1983;**20**:133-4, 'sputum' should read 'serum' in the last line of the Summary.