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Absence of IgA and growth hormone deficiency associated with short arm deletion of chromosome 18

We report a boy with short stature, minor somatic anomalies, slight mental retardation, deficiency of immunoglobulin IgA, and deficient growth hormone (GH) secretion. He has only 45 chromosomes, with a translocation involving the pairs 13 and 18, resulting in a short arm deletion of chromosome 18, as demonstrated by a modified Giemsa staining technique (Sumner, Evans, and Buckland, 1971).

Case report

The boy, now 12 years old, was born to a 39-year-old mother and 43-year-old father. Both parents and the 14-year-old brother are healthy and of average height. No other cases of growth failure are known in the family. The baby was delivered in brow presentation, after a long second stage of labour of 55 minutes. Respiration was rapid during the first week, but there was no other evidence for brain lesion.

The boy walked at 1·6 years, spoke a few words at 2·4 years and sentences at 6 years. He began school in a special class for slow learners at 7 years, because his level of development was estimated to be 1 year behind average. 3 years later he was transferred to a normal class. His height velocity has been subnormal from birth, and from the second year onwards his height has been from 4·0 to 4·8 SD below the mean for age. His bone age has lagged from 1·0 to 1·5 years behind his chronological age.

The boy (Fig. 1) has ptosis of left upper lid and convergent squint of the left eye with amblyopia. The auricles are large and protruding. The neck is short with slight pterygia and with left-sided torticollis. The shoulders and the thoracic cage are broad and 'Turner-like', with widely spaced nipples. The

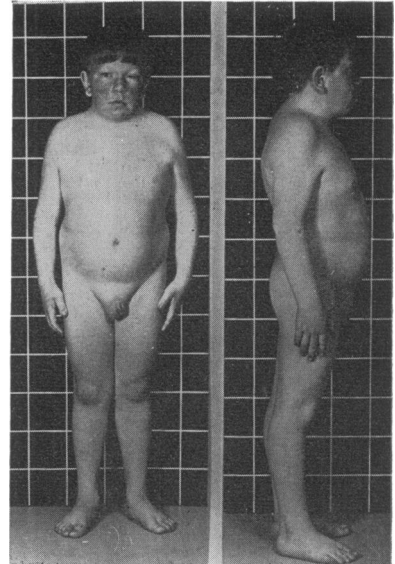


FIG. 1.—The patient at the age of 12·4 years.

extremities are normal, as is the penis; the testes are of normal size, 4·5 ml at 12·4 years. The dermatoglyphs of the palms are normal. No signs of puberty have appeared as yet. He has enjoyed good health without any increased susceptibility to infections.

Cytogenetic studies. Peripheral blood lymphocyte cultures and karyotype analysis of the patient and his parents have been described (Leisti, 1971). Both parents had normal karyotype. The patient had only 45 chromosomes; one chromosome was missing from pair 13 and another from pair 18, while an additional chromosome was present in group C. Detailed analysis of the banding patterns of 15 cells showed that the long arm of this additional chromosome had a band pattern typical of the long arm of chromosome 13, and that the short arm had a pattern typical of the long arm of chromosome 18. Characteristically, the very proximal paracentric region of the long arm (Fig. 2) constantly had a distinct band typical of chromosome 13, suggesting that the long arm of chromosome 13 had remained intact in the process of translocation and that most or all of the short arm of chromosome 18 had been lost.

Immunological studies. Methods used in the immunological studies have been described earlier (Savilahti, 1972). The absence of serum IgA was verified on several occasions (below 0·06 mg/100 ml). Serum IgM and IgG concentrations were normal. The other members of the family had normal serum immunoglobulin levels. Jejunal and rectal biopsies showed no IgA-containing cells in the mucous membranes, whereas an excess of cells containing IgM was present. IgA was absent from the saliva and jejunal

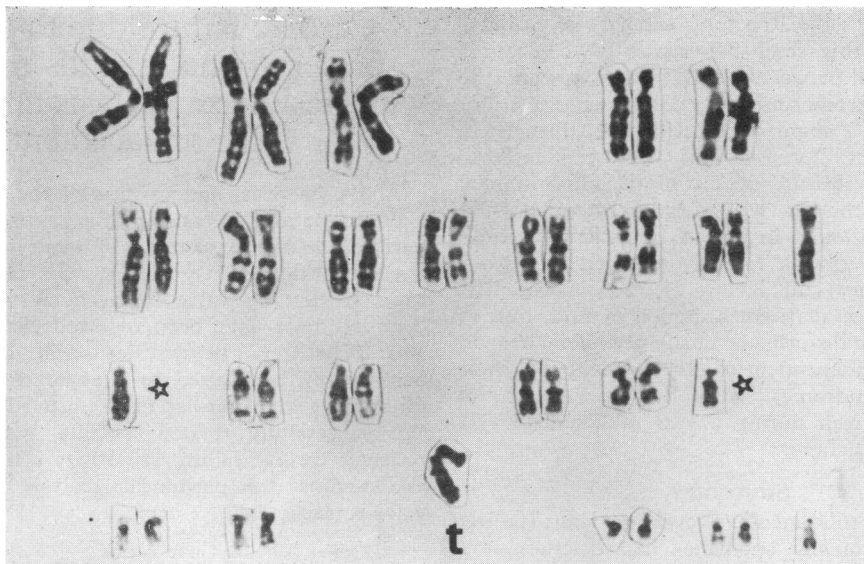


FIG. 2.—Karyotype of the patient: 45,XY,13-,18-,t(13q:18q)+. The missing chromosomes are indicated by asterisks and the chromosome with translocation with the letter 't'.

fluid. The concentration of IgM was increased in the jejunal fluid, whereas only IgG was detected in the saliva. The boy's production of both circulating and local IgA appeared severely depressed or totally absent. A defect in the cell-bound immunity is unlikely in view of the normal lymphocyte counts, the normal reaction of the lymphocytes to PHA stimulation, and the normal reactions to tuberculin (BCG) and smallpox vaccinations.

Endocrine studies. Plasma GH concentration was determined by radioimmunoassay; dextran-coated charcoal was used to separate bound and free hormone. The standard preparation, NIH-GH-HS 1216c, had growth activity of 1.45 IU/mg.* The minimum normal response to insulin hypoglycaemia and to arginine is 7.0 ng/ml. The boy's ability to secrete growth hormone (GH) was studied on three occasions by insulin hypoglycaemia test. The lowest blood glucose concentrations were 33, 44, and 39 mg/100 ml, or 49, 71, and 51% of the basal concentration. The highest plasma GH levels were 2.0, 1.0, and 2.4 ng/ml. On intravenous arginine infusion, 0.5 g/kg, the highest plasma GH level was 2.4 ng/ml. When hypoglycaemia and arginine tests were repeated during constant infusion of propranolol (80 µg/min) and epinephrine (0.1 µg/kg per min), the highest plasma GH level obtained was 4.5 ng/ml (lowest blood glucose was 28 mg/100 ml or 41% of basal concentration). In a short metabolic GH test (Prader *et al.*, 1964), the urinary

excretion of nitrogen during 5 days of GH treatment was 46% of the excretion during a similar pretreatment period, an exceptionally high response providing strong evidence for deficient GH secretion. The spermidine to spermine molar ratio of blood cells, determined on two occasions, was very low, 0.31. This polyamine ratio correlates directly with the GH activity in children (Siimes *et al.*, 1972).

The boy was given GH treatment for 12 months, 4 mg twice weekly. Two Roos preparations were used, both of which have given good catch-up growth responses in our GH-deficient patients. No acceleration was obtained in this boy's growth velocity as compared with the pretreatment year or the 4-month period immediately after the treatment.

The plasma thyroxin concentration was normal, 6.6 µg/100 ml. The mean basal rate of excretion of 17-ketogenic steroids was 2.3 mg/m² per 24 hr, and a peak of 7.4 mg/m² per 24 hr was obtained during the first day of metyrapone administration. Normal ACTH secretion was further confirmed by the response of plasma cortisol during insulin hypoglycaemia; the highest levels were 37, 46, and 29 µg/100 ml in the three tests performed. As the boy also shows normal pubertal growth of the testes (see above) there was evidence of normal secretion of all pituitary trophic hormones.

Comments

The clinical picture of our patient is fully compatible with the syndrome associated with deletion of the short arm of chromosome 18 (De Grouchy, 1969), the absence of IgA probably also being

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connected with the structural anomaly of chromosome 18 in this case (Stewart *et al.*, 1970). A causal relation between the GH deficiency and the deletion of chromosome material is suggestive, but the association could be coincidental. Deficiency of a pituitary hormone has not been hitherto reported as a feature of any of the chromosomal syndromes, though a probably impaired GH response was found in one of 12 patients with an autosomal aberration recently reported by Ruvalcaba, Thuline, and Kelley (1972). Apparently, our patient has deficient secretion of GH, but, in addition some disturbance of the peripheral growth mechanism independent of GH deficiency (such as in 45,X syndrome), since no acceleration of growth was seen during a year of adequate GH substitution therapy.

Summary

A boy with mild mental retardation, short stature, and minor somatic anomalies had deletion of a short arm of chromosome 18, due to a translocation. Immunoglobulin IgA was absent in blood plasma and intestinal mucosa. Growth hormone was deficient after repeated insulin and arginine testing, and nitrogen retention test. There was no acceleration of growth after growth hormone treatment for 12 months.

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Cardiac failure due to acute bacterial endocarditis treated with peritoneal dialysis and aortic valve replacement

Active bacterial endocarditis of the aortic valve is often fatal due to cardiac failure caused by leaflet perforation and weakening of ventricular muscle from infiltrating myocarditis. So far 61 adult cases treated by valve replacement with a 70% complete cure have been reported (Sarot, Weber, and Schechter, 1970). Peritoneal dialysis has occasionally been used to prepare these patients for surgery when cardiac failure proved intractable. We successfully treated a child with diuretic-resistant cardiac failure caused by active bacterial endocarditis by peritoneal dialysis and aortic valve replacement.

Case report

A previously healthy 12-year-old boy developed fever, splenomegaly, aortic insufficiency, and congestive cardiac failure. 3 blood cultures grew penicillin-resistant *Staphylococcus aureus* and he was treated with 18 days of intravenous oxacillin, after which 4 blood cultures were sterile and he was afebrile. 3 months after the onset of this illness he was transferred to the Hospital for Sick Children, Toronto, because of intractable cardiac failure.

On admission he was pale, orthopnoeic, and in marked cardiac failure; pulses were bounding and blood pressure was 114/55 mmHg. There was a grade 1/4 ejection systolic murmur and a grade 3/4 early diastolic murmur at the lower left sternal border. His liver was palpable 6 cm below the right costal margin and tender. ECG showed marked left ventricular hypertrophy and ischaemic changes over the left precordial leads. Chest x-ray showed massive cardiomegaly with a 70% cardiothoracic ratio. There was no clinical evidence of active endocarditis; there was no fever or splenomegaly, and 5 blood cultures were negative. He responded initially to digoxin, frusemide,* and spironolactone, but 5 days after admission his cardiac failure became rapidly and progressively more severe; cardiomegaly increased, urine output decreased, and persistent hyponatraemia and hypochloreaemia developed. An intravenous 'cocktail' of frusemide, acetazolamide, aminophylline, and an intramuscular injection of mercuhydrin failed to produce diuresis. Aortic valve replacement became a matter of urgency.

Because he was refractory to conventional decongestive measures, and because his electrolyte disturbance persisted, the patient underwent peritoneal dialysis with a commonly available dialysis solution† to which 5 mEq/l. of KCl had been added. 500 cm³ of this

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†Dianeal—Baxter Laboratories of Canada Ltd., Malton, Ontario.