alert, and sat unsupported. She plays with toys and has two clearly recognizable words. Muscle tone is normal and there is no weakness. She continues on biotin 5 mg twice daily.

Discussion

Hypotonia was a striking clinical feature in our patient and has been noted before in one of the three published reports of this condition. Eldjarn et al. (1970) described a 41-month-old infant whose muscular hypotonia and retarded motor development was severe enough to consider the diagnosis of Werdnig-Hoffmann disease. The other two reports (Gompertz et al., 1971, 1973) do not mention hypotonia but both patients had metabolic acidosis associated with a variable neurological picture ranging from abnormal behaviour and irritability to coma and delayed motor development. However, the patient described by Gompertz in 1971 is now thought to have had a defect in β-methylcrotonyl CoA carboxylase activity secondary to a more generalized defect in biotin metabolism (Gompertz, 1974).

The mechanism of the hypotonia in our child is not known. Organic acids have been shown to be encephalopathic in rabbits when infused intravenously, causing sleep and excess of slow wave activity on the electroencephalogram (White and Samson, 1956). A similar peripheral effect at the level of the spinal cord, neuromuscular junction, or within the muscle itself cannot be excluded. Hypotonia is also a feature of some other inborn errors of organic acid metabolism—methylmalonic aciduria (Gompertz, 1974) and propionic acidemia (Hommers et al., 1968, Gompertz et al., 1970). It is interesting that glycine, an inhibitory neurotransmitter, is often raised in the plasma of patients with propionic and methylmalonic acidemias and it is tempting to speculate that glycine may be responsible for the hypotonia in these conditions. This, however, seems unlikely in our patient since the plasma glycine was normal.

Although symptoms became apparent in our patient at the time of an intercurrent infection and coincided with the dietary protein increase, we have not imposed any protein restriction because of the excellent clinical and biochemical response to biotin therapy.

Metabolic disease, especially the organic acidemias, must be considered in the differential diagnosis of the floppy infant syndrome. The responsiveness of several of the organic acidemias to protein restriction, and/or massive doses of the appropriate vitamin, shows that though these inborn errors probably account for only a very small proportion of the floppy infants, these children are treatable if the diagnosis is made.

Summary

A floppy infant is described who has an inborn error of organic acid metabolism due to defective activity of the enzyme β-methylcrotonyl CoA carboxylase. She presented with hyperventilation, hypotonia, and regression of motor and intellectual development. She responded to treatment with biotin.

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REFERENCES


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Balanced translocation, impaired sperm motility, and offspring anomaly

This communication reports an example of a father with a balanced translocation who produced an abnormal child with a similar translocation after treatment for a low sperm motility.

Case report

A 27-year-old Pakistani woman had 5 spontaneous, unexplained, first trimester abortions. Her husband showed no physical abnormality, but had a sperm motility of only 5% in a total count of 110 million. During
treatment with fluoxymesterone, and then mesterolone, which improved his motility to 75%, his wife conceived. Pregnancy was uneventful until 25 weeks of gestation when hydramnios was noted. This persisted until 36 weeks of gestation when spontaneous rupture of membranes occurred, and labour progressed, leading to caesarean section being performed for fetal distress. An obviously abnormal infant was delivered weighing 3·52 kg.

The abnormalities were a midline cleft of the hard and soft palate; low set, prominent, and unduly hairy auricles which also showed a third helix; epicanthic folds; enlargement of both liver and spleen 3 fingers breadth below the costal margin; a single left palmar crease; soft tissue syndactyly of the left and right second and third toes; generalized gross oedema; and an unusual large myxoedematous swelling over the nape of the neck (Fig. 1a). A generalized petechial rash developed at 9 hours of age.

Investigations showed a platelet count of 21 000/mm³. Maternal platelets were 210 000/mm³ without the presence of platelet antibodies. There was no history of ingestion of medicaments during pregnancy. Investigations for cytomegalovirus, toxoplasma, and rubella were negative. Skull x-ray showed a hypercalcified and deformed occiput (Fig. 1b). The leucocyte alkaline phosphatase score was normal.

Progress. At 7 days of age the generalized oedema and suboccipital swelling subsided and the liver and spleen were no longer enlarged. Despite tube feeding the weight had fallen to 3·06 kg. The infant first smiled at 13 weeks of age, by which time the weight had reached only 3·7 kg. The presence of a systolic murmur suggestive of a ventricular septal defect was noted but the electrocardiogram and chest x-ray were normal. The head circumference was 36 cm (<3rd centile for age) and marked hypertonia was present. The infant was socially unresponsive but the fundi were normal, and the baby appeared to hear. The platelet count was 302 000/mm³.

Cytogenetics. Trypsin banding (Seabright, 1971) of blood and fibroblast preparations showed that material from the distal part of the long arm of a no. 22 chromosome was translocated onto the long arm of a no. 11 chromosome, resulting in a balanced translocation, t (11; 22) (q 23; q 11). Banding of the father’s blood showed a similar translocation, while the mother had a normal karyotype (Fig. 2).

Discussion

This patient appears to share the following features with reported cases of deleted and ring 22 chromosomes (Nelson, 1972; Warren, Rimoin, and Summit, 1973; Margenis et al., 1972): epicanthic folds, hypotonia, mental/developmental retardation, a degree of microcephaly, prominent low set ears, and cutaneous syndactyly of digits. Warren and Nelson’s cases showed a high arched palate, but no other case showed a haematological disorder.

The clinical picture suggested an unbalanced translocation, and more specifically a terminal deletion of the long arm of the 22 chromosome. However, the banding patterns indicated a balanced translocation in the infant, as in the father, who is phenotypically normal. Since balanced translocations are not usually associated with an abnormal phenotype, the chromosomal defect seen in the infant must in some way be different from that of the father, unless the translocation and the clinical malformation are coincidental.

This may seem unlikely also in view of the recurrent abortions which one is tempted to attribute to the production of autosomally imbalanced zygotes. Another interesting aspect is the balanced...
frequency of chromosomal abnormalities after induced ovulation.

The chromosomal defect was present before treatment in this case, and while the number of childless couples presenting for investigation and treatment makes chromosomal analysis in each case prohibitive, some particularly unusual feature of these couples, for example an otherwise unexplained history of recurrent abortion, could be considered an important indication for chromosome analysis of both partners. A balanced chromosomal rearrangement in one parent does not exclude the couple from having normal children, but amniocentesis for chromosomal analysis should be considered by the couple if termination of pregnancy is acceptable in the event of an abnormal chromosomal complement being found. However, the problem highlighted by this case suggests that special caution should be exercised in counselling even when a seemingly balanced rearrangement, resembling that of the carrier parent, is found in the fetal cells. This couple have decided against amniocentesis, and artificial insemination by a donor is unacceptable to them.

Summary

An infant with multiple physical abnormalities, failure to thrive, and mental deficiency, all probably due to a 22/11 chromosomal translocation is described, and the implications of inducing pregnancies in childless couples are discussed.

We thank Professor I. D. Cooke for permission to present this case.

References


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