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theory remains speculative as the animal studies have shown no evidence of strings or bands as the cause of the limb deficiency. If the vascular compromise occurred at the time of premature rupture of the membranes there would be adequate time for healing of lesions and resorption of amputations. Healing in the fetus is particularly fast and relatively non-scarring. It is likely that this child's limb defects were related to amnion rupture, and are not associated with Van der Woude syndrome.

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References

Fetal valproate phenotype is recognisable by mid pregnancy

Sir,
In the November 1987 issue of your journal, Winter et al reported four infants who were exposed to sodium valproate or valproic acid during pregnancy. Three surviving infants showed the characteristic facial features of the fetal valproate syndrome described by DiLiberti et al and confirmed by several authors. We report here a 22 week fetus with a large myelomeningocele and similar facial abnormalities.

The mother of this subject, a 23 year old primigravida of Iberian origin, attended a psychiatric clinic and suffered from grand mal epilepsy. She received sodium valproate (500 mg twice a day) from the age of 18 years in combination with clobazam (10 mg, three times a day). When she became pregnant, she was referred to us for prenatal diagnosis of open neural tube defect.

At 18 weeks of gestation, serum and amniotic α fetoprotein (AFP) concentrations were evaluated by radioimmunoassay. Maternal serum AFP was raised (2.9×MoM). The amniotic fluid, obtained by amniocentesis, was clear and blood free, with an AFP concentration within the normal range (<3 MoM). Ten ml of amniotic fluid were centrifuged at 14 000 g for five minutes to remove any red cell membrane contamination. Quantitative measurements of acetylcholinesterase on unfrozen material
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There was an elongated spina bifida aperta (30 mm) involving five lumbar and two sacral vertebrae with spinal cord showing in the upper part. The spinal cord was open and spread out. In the lower part, only the filum terminale was visible (figs 1 and 2). There was a brachycephalic skull and facial peculiarities (fig 3) including bulging ocular globes, infraorbital grooves, broad and flat nasal bridge, increased inner canthal distance (20 mm), very long upper lip, thin vermilion borders, small oral opening, and prominent antihelices of the ears. No visceral abnormality was found. The cerebellum was small and partially penetrating the foramen magnum, simulating an Arnold-Chiari malformation. The fresh brain weighed 51 g. Frontal sections of the brain after fixation showed enlargement of the lateral and third ventricles.

An open neural tube defect was detected in the fetus by positive maternal serum AFP levels and by two bands on acetylcholinesterase electrophoresis of the amniotic fluid. It should be noted that the amniotic fluid concentration of AFP and acetylcholinesterase activity were within normal limits.

Owing to the difficulty of evaluating a fetal face, the existence of a valproate phenotype could be questioned in our case. However, there was such a markedly typical abnormal facial appearance that it was immediately attributed to the sodium valproate therapy taken by the mother. Thus, as might be logically expected with a teratogen, the valproate phenotype is already apparent by mid pregnancy.

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