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CASE REPORT

Failure of periconceptual folic acid to prevent a neural tube defect in the offspring of a mother taking sodium valproate

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INTRODUCTION

The risk of having a baby with a neural tube defect (NTD) for women taking sodium valproate (VPA) is about 2%[1], or at least 60 times the background risk in the UK. Since this is similar to that for recurrence of a NTD in someone who has previously had a baby with this condition, for whom high-dose periconceptual folic acid (4 mgs/day) is known to offer considerable protection[2], it has been suggested that women on VPA should take a similar high-dose periconceptually. We report the case of a woman exposed to VPA who gave birth to an infant with an NTD, among other malformations, despite taking high-dose folic acid periconceptually and emphasize there is no evidence that folic acid in any dose protects against NTDs caused by VPA.

CASE REPORT

A baby boy was delivered to a 26 year old woman following a planned pregnancy. The child had a lumbosacral NTD, small ventricular and atrial septal defects, a cleft of the soft palate, bilateral talipes and features consistent with foetal valproate syndrome. Chromosomal analysis demonstrated a normal male karyotype. The NTD and cleft palate were subsequently repaired.

The mother, who was otherwise well, had presented aged 16 years with a 2 year history of prolonged absence seizures and an EEG showing features in keeping with primary generalized epilepsy. She was prescribed VPA 500 mg BD (twice daily) and became seizure free. Four years later the seizures returned and the dose of VPA was increased to 1000 mgs twice daily. The married woman, who at the age of 23 had been seizure free for 4 years, was prescribed 4mg/day folic acid. She remained seizure free and 18 months later became pregnant. She stopped the folic acid at the end of the first trimester. There was no family history of birth abnormalities. Foetal ultrasound during the pregnancy had raised no concerns.

DISCUSSION

Sodium valproate was the probable cause of the malformations, as all have been described with this drug[3], the NTD was in the typical site for VPA[4], and the child had features of foetal valproate syndrome. A NTD has not, to our knowledge, previously been described in an infant born to a woman on VPA while taking periconceptual folic acid and implies that folic acid either provides incomplete protection against NTDs caused by VPA or may not work at all. Experimental evidence suggests both; in humans the neural tube is thought to

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close at five or more sites[4]. Folic acid appears to influence closure of these differentially, having the greatest effect on sites one and two corresponding to lumbar and anencephalic defects, respectively[4]. Lumbosacral defects corresponding to site five are the commonest area of abnormality associated with VPA[4]. There is no consistent evidence from animal studies that supplementation with folate or its derivatives reduces the rate of valproate-induced NTDs[5–8]. VPA also reduces serum folate levels in humans to a much lesser extent than other AEDs, which are less often associated with NTDs[9, 10].

It has been postulated that folic acid prevents between 50 and 70% of all NTDs[11–13]. None of the studies on which these figures are based have investigated the protective role of folic acid supplementation in women exposed to VPA. To determine if this is the case would require a controlled trial. Although unethical to include a placebo group, since low-dose (0.4 mgs/day) periconceptual folic acid reduces the background incidence of NTDs[14], it would be possible to compare the effects of low- and high-dose folic acid. Until firmer evidence is available, women taking VPA should continue to take folic acid before and during pregnancy for the same reasons as those women not on VPA. Doctors should not be reassured that infants exposed to VPA *in utero* will not develop NTDs and should monitor such pregnancies with appropriate use of alpha fetoprotein blood sampling, foetal ultrasound and amniocentesis.

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