Case Report

Foetal valproate syndrome; the risk is still out there: A case report

J. C. Ranasinghe[1*], M. M. Manamperi[1], R. C. Ediriweera[1]
[1]Lady Ridgeway Hospital for Children, Colombo, Sri Lanka.

Abstract

Sodium valproate should be used cautiously in women belonging to the child-bearing age due to the potential teratogenicity of the drug. It has been found that mothers who had taken sodium valproate during pregnancy have delivered babies with foetal valproate syndrome, evident by the features such as intrauterine growth retardation (IUGR), suggestive facial features, microcephaly, cardiac and eye anomalies, learning disabilities and developmental delay. We report a patient with late diagnosis of foetal valproate syndrome whose mother had taken 1000 mg/ day of sodium valproate throughout the pregnancy. In addition to the characteristic facial features, she had bilateral corneal clouding, small joint contractures with early clawing and partial anomalous pulmonary venous drainage (PAPVD). This cardiac anomaly has not been well described in literature. This case highlights the importance of active surveillance of teratogenic side effects early in the life.

Keywords: Intrauterine growth retardation (IUGR), Partial anomalous pulmonary venous drainage (PAPVD), Occipito Frontal Circumference (OFC), Ventricular septal defect (VSD)

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*✉ **Correspondence:** c.ranasinghe0323@gmail.com, http://orcid.org/0000-0002-1586-2987

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Introduction

There is an increased incidence of major and minor congenital malformations among children born to epileptic mothers [1]. The effect of the antiepileptic drugs and the effect of epilepsy itself may contribute to these negative outcomes. Sodium valproate is a very effective antiepileptic drug recommended for use in idiopathic generalized epilepsy [2]. The prescription of valproate in women of childbearing age should be done cautiously because of the potential teratogenicity of the drug. There is a trend towards more severe malformations with exposure to valproate doses of 1000 mg/ day or higher in the first trimester as monotherapy or polypharmacy [3]. We report an 18-month-old girl with foetal valproate syndrome born to a 35-year-old mother who was on sodium valproate 1000 mg/ day combined with levetiracetam 1000 mg/ day and clobazam 10 mg/ day for three years duration, which had been continued throughout the pregnancy.

Case report

An 18-month-old girl, the second child of non-consanguineous parents having a healthy firstborn child, was admitted to evaluate global developmental delay. The mother, a symptomatic epileptic patient since five years of age, was on carbamazepine initially and was changed over to sodium valproate 500 mg bd, levetiracetam 500 mg bd, and clobazam 10 mg daily for the last three years. Her second pregnancy ended in a miscarriage at 26 weeks of gestation. The third pregnancy (current baby) was an unplanned pregnancy, detected at eight weeks of period of amenorrhoea (POA). The baby was delivered by elective lower segment caesarean section at 38 weeks gestation considering intrauterine growth retardation (IUGR) and the previous bad obstetric history. The birth weight was 2.0 kg. She was admitted to the neonatal intensive care unit for further management after resuscitation at birth due to poor respiratory effort.

The baby was noted to have cyanosis and was detected to be having a murmur on the second day of life. An echocardiogram was arranged. She was able to breastfeed and was discharged on the fifth day of life after arranging follow-up care at the local paediatric clinic. At one year of age, she was referred to the tertiary care hospital for ophthalmological evaluation and was detected to have bilateral corneal opacities. The baby was referred for medical evaluation and noted to have failure to thrive, microcephaly, and global developmental delay with features suggestive of foetal valproate syndrome. The facial features were narrow bifrontal diameter, high forehead, epicanthic folds, a broad low nasal bridge, anteverted nostrils, and a long philtrum. She had small joint contractures of the third and fourth fingers, indicating early clawing of hands. Her cardiac anomaly was partial anomalous pulmonary venous drainage with drainage of one right upper pulmonary vein into the right atrium-superior vena cava junction. The ophthalmic evaluation confirmed bilateral corneal opacifications (Figure 01). She had significant developmental delay indicating a developmental age of one year at eighteen months chronological age. The weight was 6.5kg (less than -3SD), height 75cm (less than -2SD), and occipitofrontal circumference (OFC) 42cm (less than 3rd centile), indicating failure to thrive with no evidence of nutritional deficiencies or chronic ill health.

The biochemical and haematological evaluation revealed haemoglobin 11.6 g/dL, liver function tests Alanine Transaminase (ALT) 35U/L, Aspartate Transaminase (AST) 73U/L, Albumin 44g/L, and renal functions tests (Sodium 136 meq/L, Potassium 3.7 meq/L, Blood urea 5 mg/dL, Creatinine 44 mg/dL). The urine culture was sterile, and the blood gas analysis was within the normal range. The X-ray spine and chest showed no vertebral or rib anomalies.

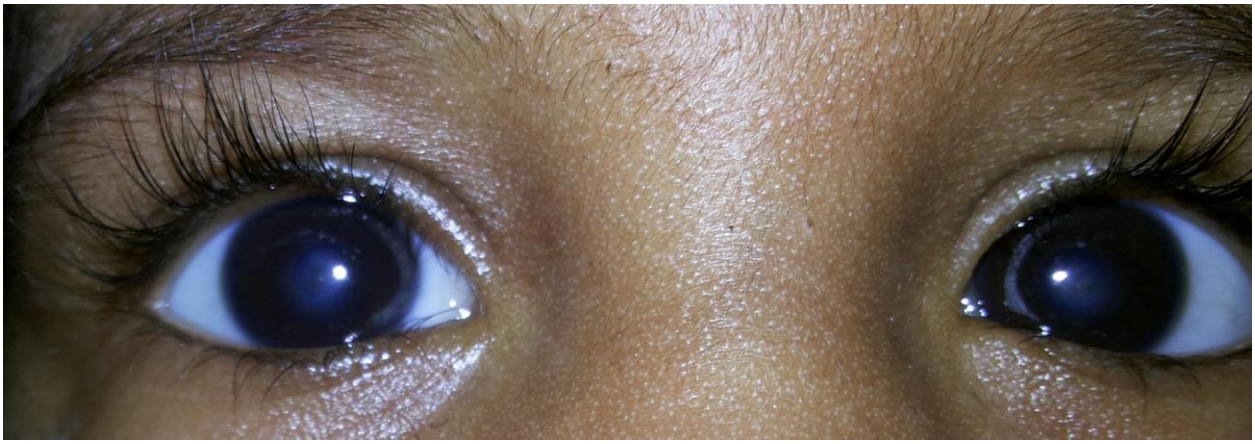

Figure 01: Bilateral corneal opacifications and broad nasal bridge observed in the child.

Discussion

We report a child with the foetal valproate syndrome. This child had IUGR with typical facial features, microcephaly, global development delay, and corneal opacifications, small joint contractures, and partial anomalous pulmonary venous drainage. The valproate syndrome was confirmed. Although the child had a congenital cardiac abnormality, this has not been reported in the previous literature associated with valproate syndrome.

Sodium valproate teratogenicity was first discussed in 1980 by Dalens and Raynaud and formally reported in 1982 by Robert and Giband [4,5]. DiLiberty *et al.* introduced the term foetal valproate syndrome in 1984 [6]. There are numerous case reports and case series stating the teratogenicity of valproate usage in women of childbearing age [3,7,8].

The use of anticonvulsants as mono-therapy or poly-pharmacy during pregnancy is associated with an increased risk of malformations and developmental delay in children [3]. The risk is more when sodium valproate is given more than or equal to 1000 mg per day with or without other antiepileptic drugs. Characteristic dysmorphic features and malformations have been described with foetal exposure to phenytoin, valproate, and carbamazepine [8]. Valproic acid (VPA) is a broad-spectrum anticonvulsant, and it crosses the placenta readily with higher serum concentrations in the foetus than in the mother [8]. The teratogenic effects of valproic acid are categorized as stillbirths, intrauterine growth restriction, major and minor abnormalities, and cognitive

and behavioural impairment. The facial features of foetal valproate syndrome include epicanthic folds, infra-orbital groove, a medial deficiency of the eyebrows, a flat nasal bridge, a short nose with anteverted nares, a smooth or shallow philtrum, a long thin upper lip, a thick lower lip, and a small, downturned mouth [8,9].

Our patient had supportive facial features with a narrow bi-frontal diameter, high forehead, epicanthic folds, broad low nasal bridge, anteverted nostrils, and a long philtrum. The cardiovascular anomalies described are aortic coarctation, hypoplastic left heart syndrome, interrupted aortic arch, ostium secundum atrial septal defect (OS ASD), pulmonary atresia without ventricular septal defect (VSD), and perimembranous VSD (9). This baby had partial anomalous pulmonary venous drainage with the right upper pulmonary vein draining into the right atrium-superior vena cava junction, which is not well described in the literature. The limb anomalies described are long thin fingers and toes, small joint contractures, and hyperconvex fingernails [9]. Our patient had small joint contractures involving the 3rd and 4th fingers of both hands, with the right hand more prominently affected. The other main features were corneal opacities, growth retardation, and learning disabilities, which were present in our patient. Other eye features like cataract, cleft palate, hearing loss, and, to date, inguinal or umbilical hernias were not found in this patient [9].

The reported risk of congenital malformations after exposure to valproic acid during pregnancy is 10 – 11% though it can go up to 24% with increasing dose [4, 10]. Thus, it is recommended to avoid valproate during pregnancy as much as possible and to consider alternative antiepileptics, and to educate the mother about all possible side effects if it is to be continued [10,11]. The consensus statement made by the European reference network for congenital malformations and intellectual disability recommends the following four key recommendations in the management of epilepsy in pregnancy. Firstly, VPA must not be used for the treatment of migraine or bipolar disorder during pregnancy. Secondly, VPA must not be used to treat epilepsy during pregnancy unless there is no other effective treatment available. Women requiring VPA treatment should be supported and counselled. Thirdly, VPA should not be prescribed to any girl or woman able to have children unless she is on a Pregnancy Prevention Programme. This will include an assessment of the potential to become pregnant, pregnancy tests before starting and during treatment, counselling about the risks of VPA treatment and the need for effective contraception whilst on treatment, review of treatment by a specialist at least annually, and signing of a risk acknowledgement form. Fourthly, women and girls who have been prescribed valproate should not stop taking their medicine without consulting their doctor as doing so could result in harm to themselves or to an unborn child [10].

Though foetal medicine is a new entity to Sri Lanka, today, it is being meticulously monitored by obstetricians and foetologists to identify foetal malformations. However, even with major abnormalities at the moment, medical termination of pregnancy for the interest of an abnormal foetus is not legalised in Sri Lanka [12]. This mother, a symptomatic epileptic patient since five years of age, was on polytherapy for the last three years, including the pregnancy. The pregnancy was identified at eight weeks of POA, mother had to continue all three antiepileptics to be symptom-free throughout the pregnancy. Although this case report reveals an unfortunate established teratogenic effect of valproate exposure during pregnancy, there may be many that can be prevented by meticulous and multidisciplinary team management of women with epilepsy.

Conclusion

In conclusion, this case report highlights the importance of avoiding sodium valproate during pregnancy due to the potential teratogenic effects. However, if it is necessary to give due to medical reasons, it is mandatory to arrange early neonatal follow-up to assess complications related to severe teratogenic effects of valproate and other anti-epileptics.

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