Published in final edited form as:

Clin Dysmorphol. 2014 April ; 23(2): 74–75. doi:10.1097/MCD.0000000000000028.

Letter To The Editor; Ocular coloboma and Fetal Valproate Syndrome: Four further cases and a hypothesis for aetiology

A Jackson¹, A Fryer², V Clowes³, and J Clayton-Smith⁴

¹University of Manchester, Medical School, Manchester M13 3PT

²Mersey Regional Genetic Service, Royal Liverpool Children's Hospital, Liverpool L12 2AP

³Clinical Genetic Service, North West London Hospitals NHS Trust, Watford Rd, Harrow, HA1 3UJ

⁴Manchester Centre For Genomic Medicine, Central Manchester University Hospitals, Manchester M13 9WL

Abstract

We read with interest the case report from Shah et al. (2014) hypothesising that coloboma may be a feature of the Fetal Valproate Syndrome (FVS). We have observed four further individuals who presented with ocular coloboma following exposure to sodium valproate (VPA) in utero and believe that this is a true association.

Patient 1

This child, a female was initially seen at 7 months of age. She was the second child of unrelated parents. Her mother had epilepsy but both parents were otherwise in good health. She was referred for assessment because of mild delay in gross motor development. During pregnancy her mother took 1000mg VPA daily and was seizure free. A previous pregnancy whilst taking 500mg VPA daily had resulted in the birth of a healthy boy. No abnormalities were noted on antenatal scans and she was born at term weighing 3.83kg (50–75th centile). On examination she had a broad forehead, a broad flat nasal bridge, a slightly short nose with a flattened tip, a thin upper lip, downturned corners of the mouth which was small with an everted lower lip, and a slightly small jaw. Her features were considered to be consistent with VPA embryopathy. She was also noted to have a left isolated iris and choroidoretinal coloboma, however, her vision seemed unaffected by this. Seen again at age 19 months she had begun walking but was delayed in her language development. At this time, she was also referred for endocrine assessment because of obesity (BMI SDS +5.1). Her height was 86.6cm (98th centile), weight 17.1kg (above 99.6th centile) and OFC 49.4cm (91st centile). No cause was identified for the obesity. Chromosomal analysis has not been undertaken.

Patient 2

This boy was the 1st child born to an otherwise healthy mother who had epilepsy. His mother took 1600mg of VPA daily in two divided doses throughout pregnancy. He was born at 42 weeks by assisted delivery weighing 3.48kg (25th– 50th centile). He was noted at birth to have small ears, a small nose with anteverted nares, a smooth, flat philtrum, thin upper lip and downturned corners of the mouth, all features consistent with FVS. He also had torticollis, a hypospadias with a hooded prepuce and an inguinal hernia. Ocular examination

revealed a coloboma affecting both the iris and the retina of the left eye but not the optic disc and he was also myopic. Chromosome examination was normal. At 14 months of age it was noted that he was quite small. His weight was 9.56kg (10th centile), height 73cm (3rd centile) and his head circumference was 45cm (below 3rd centile). His gross motor development was at the slower end of normal range and he began to walk at 18 months. On follow-up at 5 years and 3 months he had mild to moderate learning difficulties and problems with recurrent otitis media.

Patient 3

This was a male was born to a healthy father and a mother who had had epilepsy associated with learning disability since childhood. She was taking 1500g VPA and 600mg carbamazepine daily but continued to have weekly seizures throughout pregnancy. During pregnancy, a fetal anomaly scan demonstrated a congenital heart defect. The child was born at 38 weeks gestation by Caesarean section and weighed 2.41kg (<5th centile). Following birth, examination confirmed a large atrial septal defect, which required surgical closure, a cleft palate and hypospadias. . He had a medially deviated, dorsiflexed great toe and the remainder of his toes overlapped. Facially, he had classical facial features of FVS with neat eyebrows, a short nose, flat philtrum and a downturned mouth. He was also noted to have hypertelorism and brachycephaly. A coloboma affecting the left eye was noted. Ophthalmological examination revealed that this also involved a significant part of the retina and as a result he had very poor vision in the left eye. The right optic nerve was noted to be smaller than the left and he was born with a blocked tear duct. He failed to thrive after birth and required a gastrostomy due to poor feeding. At 10 months, his OFC was 38cm and he was able to sit alone, however his gross motor development was delayed by about 4–5 months. He also had some hearing impairment . Microarray analysis was normal and no other cause for this pattern of problems apart from FVS could be recognised on genetic review.

Patient 4

This patient, a further male, has previously been reported by Mo and Ladusans in 1999. Born at 38 weeks, his mother had been taking 1000mg valproic acid daily in two 500mg doses during pregnancy. Intrauterine growth retardation was noted and the birth was assisted by ventouse extraction . He had distinctive dysmorphic features consistent with FVS: hypertelorism, flat nasal bridge, upslanting palpebral fissures, a short nose with anteverted nares, a long shallow philtrum, a downturned mouth and a thin vermilion border. He was also noted to have a right inguinal hernia, talipes equinovarus, tongue tie and a systolic murmur. Cardiac catheterisation revealed that he had an absent right pulmonary artery. Furthermore, he had bilateral iris colobomata and reduced visual acuity in the right eye. At 19 months, he was reported to have developmental delay with generalized hypotonia. His gross motor development was at the level of 10–12 months and he would bottom shuffle and crawl in place of walking. He had good fine motor skills with a pincer grasp. His speech was delayed. At the age of 2 years his weight was 9.53kg (below 3rd centile), height 78cm (below 3rd centile) and OFC 47cm (below 10th centile). Chromosomal analysis revealed a normal 46, XY karyotype.

A number of ocular abnormalities have been described in FVS. In a review by Kozma et al. (2001) 9% of FVS patients had an ocular abnormality. These included esotropia, nystagmus, tear duct anomalies, microphthalmia, cataract and corneal opacities. In a study of 46 patients with fetal anticonvulsant syndrome reported by Glover et al. (2002) 67% had ocular abnormalities, with myopia being especially common. Other abnormalities included strabismus, astigmatism, anisometropia and isolated reports of colour vision deficiency and

congenital cataract. As Shah et. al. state, coloboma is not commonly reported in cases of FVS but our observation of a further 4 affected patients leads us to suggest that it is a rare but definite manifestation of FVS. A coloboma is a developmental defect of the eye which can involve the iris, choroid, retina and optic disc. It is a rare occurrence with an incidence of fewer than 1 in 10,000. Embryologically, in the 22 day embryo, bilateral shallow grooves form out-pouchings of the forebrain to produce two optic vesicles. These vesicles then invaginate and a fissure is formed at the inferior pole called the choroid fissure. This fissure carries the hyloid artery, which will become the central artery of the retina. By the seventh week, the lips of the choroid fissure fuse to form an optic cup. Colobomata are formed when this fissure fails to close completely. Coloboma may occur as part of the spectrum of microphthalmia and in some cases complete anophthalmia may even be present. Coloboma may have a genetic basis but environmental factors are also known to be implicated in the aetiology. Maternal use of thalidomide during pregnancy, for example has been reported to be associated with coloboma as has fetal alcohol syndrome. There has been one report in the literature of exposure in utero to another AED, carbamazepine in a child with coloboma (Sutcliffe et al. 1988).

Ocular development is directed under tight molecular control, principally involving the genes *PAX6* and also *PAX2*. Mutations in *PAX6* can produce varied phenotypes including aniridia, coloboma of the optic nerve, ocular coloboma and optic nerve hypoplasia (OMIM 607108). Using *Xenopus* and zebrafish embryos, Gurvich et al (2005) demonstrated that through its action as a histone deacetylase inhibitor, VPA affected expression of a large number of developmental genes. In the eye specifically, VPA has been found to reduce expression of both *PAX6* and *PAX2*. (Pennati et al 2001, Balmer et al. 2012) In the light of this evidence we would therefore hypothesise that ocular coloboma in patients with FVS could be caused by reduction in *PAX* gene expression. Though coloboma is not a frequent finding with VPA exposure, our observation of coloboma in 4/150 patients with FVS seen in our clinic together with Shah's report suggest that it should be added to the list of possible malformations associated with in utero VPA exposure. For this reason, and because of the increased risk of other ocular pathologies, ophthalmological examination and review should be undertaken as part of the health surveillance in all children of mothers taking VPA in pregnancy.

References

- Balmer NV, Weng MK, Zimmer B, Ivanova VN, Chambers SM, Nikolaeva E, Jagtap S, Sachinidis A, Hescheler J, Waldmann T, Leist M. Epigenetic changes and disturbed neural development in a human embryonic stem cell-based model relating to the fetal valproate syndrome. *Hum Mol Genet.* 2012; 21:4104–4114. [PubMed: 22723015]
- Glover SJ, Quinn AG, Barter P, Hart J, Moore SJ, Dean JC, Turnpenny PD. Ophthalmic findings in fetal anticonvulsant syndrome(s). *Ophthalmology.* 2002; 109:942–947. [PubMed: 11986102]
- Gurvich N, Berman MG, Wittner BS, Gentleman RC, Klein PS, Green JBA. Association of valproate-induced teratogenesis with histone deacetylase inhibition in vivo. *FASEB J.* 2005; 19:1166–1168. [PubMed: 15901671]
- Komza C. Valproic Acid Embryopathy: Report of Two Siblings With Further Expansion of the Phenotypic Abnormalities and a Review of the Literature. *Am J Med Genet.* 2001; 98:168–175. [PubMed: 11223853]
- Mo CN, Ladusans EJ. Anomalous right pulmonary artery origins in association with the fetal valproate syndrome. 1999; 36:83–84.
- Shah KH, Shailaja S, Girishi KM. Is coloboma a feature of fetal valproate syndrome? *Clin Dysmorphol.* 2014; 23:24–25. [PubMed: 24263622]
- Sutcliffe AG, Jones RB, Woodruff G. Eye malformations associated with treatment with carbamazepine during pregnancy. *Ophthalm Genet.* 1988; 19:59–62.