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Establishing or Excluding a Diagnosis of Fetal Valproate Spectrum Disorder is a Multi-layered Process

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Abstract

Background

In 2017/2018, the Health Products Regulatory Authority issued new guidance on the prescription of Sodium Valproate (VPA) to female patients of reproductive age. A review was initiated of VPA exposed individuals to identify whether previously unascertained cases of VPA related Embryopathy could be identified.

Methods

Forty patients under twenty-three years of age were reviewed.

Results

Eleven (27.5%) new cases of Fetal Valproate Spectrum Disorder (FVSD) were identified. Twenty-four (60%) cases were felt not to satisfy diagnostic threshold for this teratogenic disorder. Five (12.5%) cases were indeterminate. Six of the forty patients (15%) had an alternative genetic cause of developmental delay established.

Conclusion

There is increased awareness regarding avoidance of VPA use in women of childbearing age. An equal awareness is warranted that developmental delay in the context of VPA exposure in pregnancy does not necessarily constitute a diagnosis of FVSD but that other competing diagnostic hypotheses have to be considered.

Introduction

The recognition of Sodium Valproate (VPA) as a teratogenic agent dates from 2 seminal papers (Di Liberti et al., 1984; Winter et al., 1987)[1, 2] in both of which the stream of single cases of suspected VPA related birth defects which had followed upon the first report (Dalens 1980)[3] were consolidated. Ardinger et al.[4], reviewed 15 cases and identified developmental delay or neurological abnormality as a major finding (67% of cases). The syndrome was distilled by the landmark report from Clayton-Smith and Donnai (1995)[5] whose paper identified both dysmorphic features and congenital malformations which had come to be recognised as constituent elements of the syndrome. Among the most identifiable dysmorphic facial features are trigonocephaly, infraorbital grooves, flat nasal bridge, a broad nasal root with anteverted nares and a shallow philtrum, while the more commonly associated congenital malformations include neural tube defects, congenital heart disease, cleft lip and palate and tracheomalacia. Latterly the name of the condition has been changed from Fetal Valproate Syndrome (FVS) to Fetal Valproate Spectrum Disorder (FVSD).

While the newly emerging syndrome was initially greeted with some scepticism by the Neurology community[6], this phase of uncertainty is now past and the association between the drug and the teratogenic consequences are widely accepted and recognised[7].

Epilepsy is common, 1 in 115 people in Ireland having epilepsy[8]. Accordingly, there are approximately 10,000 women of childbearing age who require management of epilepsy, including during pregnancy. This can present considerable challenge to the managing neurologist[9].

VPA is a first-generation anti-epileptic drug (AED) which is effective in the treatment of different types of epilepsy including absence seizure, myoclonic and generalised tonic colonic epilepsy. It is also used as a mood stabiliser in patients with bipolar disorders. It has also been used for acute and preventive treatment of episodic migraine. It has been used commonly in Europe since its licence in 1970s due to its high effectiveness[10].

The current risk of all forms of major congenital malformations with VPA is approximately 10% which is considerably higher than the general population and population of children with antenatal exposure to other AEDs[11].

There have been many cautionary articles about the risk benefit ratio of VPA in pregnancy[9]. Writing in this journal in 2011, one of the current authors stated his view that VPA was probably the major avoidable source of teratogenic consequence at present [7]. Stemming from these published concerns, the European Medicine Agency held a public hearing on the issue in September 2017 and new measures to avoid valproate exposure in pregnancy were endorsed in March 2018 [12]. In April 2018 the Pharmacovigilance Committee of the European Medicines Agency and the Health Products Regulatory Authority (HPRA) issued new contraindications on use of VPA[13], strengthened warnings to minimise the prescription use of this agent in pregnancy with a view to minimising future damage. According to the new regulations, valproate should not be used in female children, girls and women of childbearing potential unless other treatments are ineffective or not tolerated [12,13].

The Health Service Executive (HSE) established a follow up pathway for women of childbearing age on VPA[14]. According to this pathway all GPs should discuss contraceptive options with them, and GPs need to ensure that they are reviewed by a specialist annually. All specialists (Neurologist/ Psychiatrist) need to ensure that women of childbearing years on VPA have an annual risk assessment form completed. Women have to read, complete and sign this form during a visit with the specialist: at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant. Current estimates, based on public health data analysis, suggest that over 3000 women were prescribed VPA during pregnancy in the 40-year period 1975-2015[15].

Constituent to this revised awareness of the potential harmful effects of VPA, the HSE agreed that offspring of Mothers treated with VPA and about whom there was a concern as to whether these patients had VPA related embryopathy or attributable features thereof were referred to a specialist assessment clinic established for this sole purpose at CHI Crumlin. The purpose of this communication is to report the findings in 40 such cases assessed by the authors.

Methods

Forty patients were reviewed in the special purpose clinic following referral from GPs, Paediatricians and Neurologists from all over the country on the advice of HSE. Information was collected and systematically recorded according to a set pro forma. Evaluation was focused on maternal diagnosis of epilepsy, age when VPA was commenced and in what dose; whether it was the only AEDs or if polytherapy applied, what other medications were taken. Information regarding pregnancy was collected including pregnancy scans, foetal growth, seizures in pregnancy or any other complications. Birth history was documented including their mode of delivery, birth weight and whether small for gestational age or not. It was noted if they were breast fed or bottle fed. Symptoms of neonatal withdrawal were sought. A history of admission to neonatal unit was taken and if any intervention was needed. Developmental history including possible indicators of developmental delay was a particular focus. Detailed evaluation of pre-existing medical records was undertaken, and we noted all the previous diagnoses reached including developmental delay, autism, dyspraxia or dyslexia and the relevant community services and extant reports.

A detailed medical and family history was also taken. Clinical examination included general physical and systemic examination, growth characteristics by percentiles on growth charts.

Microarray and Fragile X testing was performed on all the children. All patients were evaluated by a Clinical Geneticist and Whole Exome Sequencing was performed with written consent. After full analysis of all the findings, some of these patients were confirmed as true cases of Fetal Valproate Spectrum Disorder, some received an alternative diagnosis not related to the VPA exposure, and some cases were indeterminate.

Results

The total number of patients seen under this HSE scheme was forty, the eldest of whom was twenty-three years and the youngest was two years of age at time of assessment. Of these eleven (27.5%) patients could clearly be established as previously unconfirmed cases of FVSD, twenty-four (60%) cases did not satisfy diagnostic criteria for that condition as currently constituted [16] and five (12.5%) cases were indeterminate.

Six patients among the twenty-four cases (25%) who did not satisfy diagnostic criteria for FVSD had an alternative diagnosis established by investigation. Three of these six cases had a demonstrable microarray abnormality, shown to be *de* novo in two and maternally inherited in the third instance, and such as to establish a high likelihood of pathogenic basis. Microarray findings which were familial or deemed benign variants were discounted.

A further three patients were shown to have single gene mutations, known or considered highly likely to be pathogenic according to standard criteria and in these patients a specific single gene causation was ascribed. All three genes identified are known to be causal of developmental delay. Details are given in Table 1.

Illustrative Cases (Maternal prescription of VPA confirmed in all instances).

Case 1 is a now twenty-three-year-old man born with unexpected lumbosacral spina bifida, managed surgically. He subsequently required a Ventriculo-Peritoneal shunt and had four subsequent re-siting procedures for his shunt. He now weight bears in a static position but essentially needs a wheelchair for most daily activities, has no sphincter control and has had a limited response to intensive educational input. He is almost wholly reliant on his mother, his main carer. Clinically he has many features described in association with VPA exposure (Figures 1 and 2) including bilateral hypoplasia of the thenar eminence and thumb digitisation, slightly short palpebral fissures and malar flattening. Given the spina bifida and facial features, albeit mild, a diagnosis of FVSD was made.

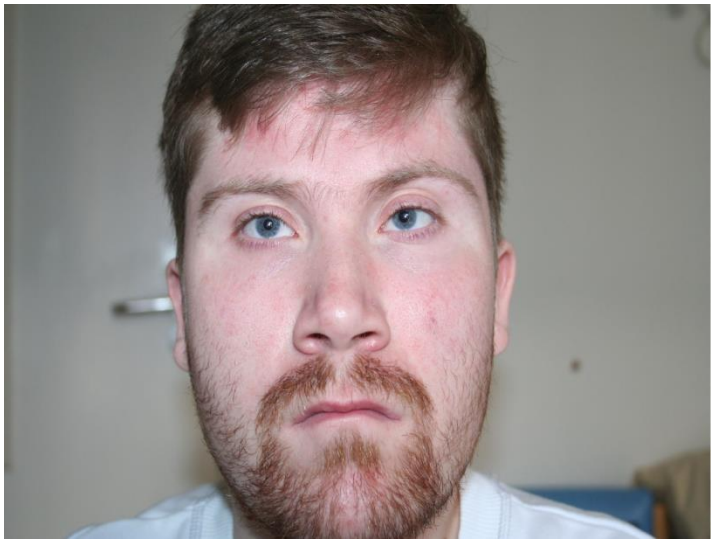

Figure 1.

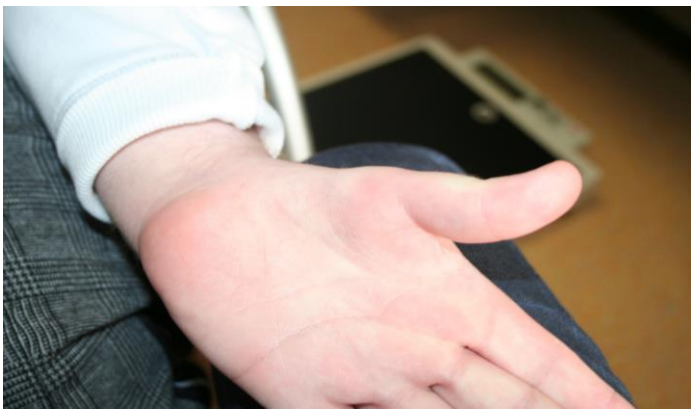

Figure 2. *(a)-Left Hand*

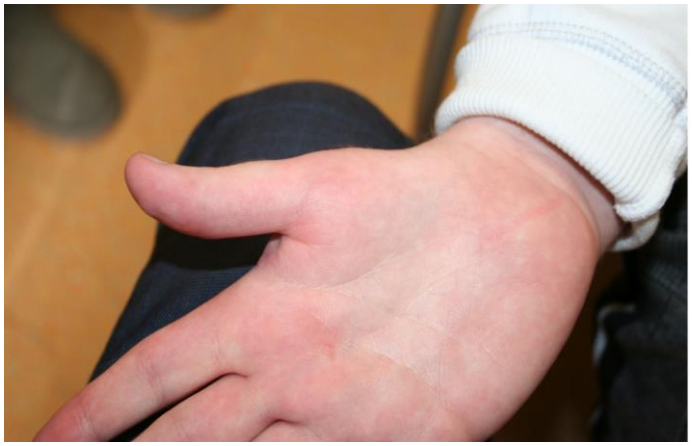

Figure 2. *(b)-Right Hand*

Case 2 is a now nine-year-old boy who presents with significant developmental delay. His speech was slow, he now attends a special Autism Support Unit in school, is somewhat clumsy in motor evaluation and has marked joint laxity clinically at the elbows but not involving other joints – Beighton score 2/9. The hands, specifically the thumbs are normal. His facial characteristics are demonstrated (Figure 3) with small palpebral fissures, epicanthic folds (R >L), broad nasal root, featureless philtrum and thin upper lip. It was considered likely that his condition represented FVSD.

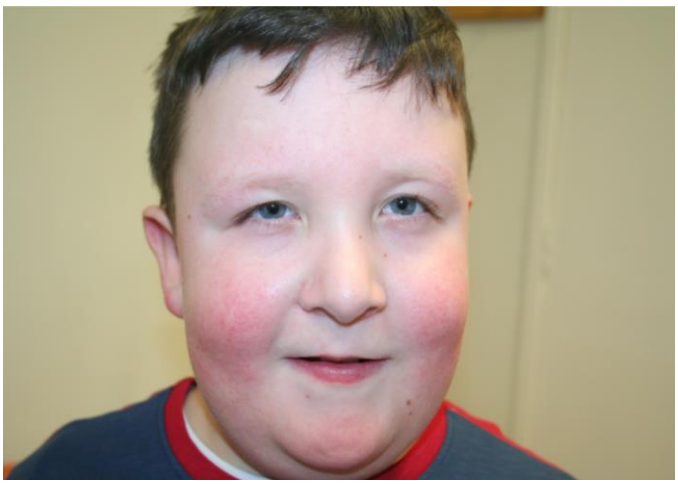

Figure 3.

Case 3 is a seventeen-year-old man, described as severely intellectually impaired and who has always been in special education. He is non-verbal, has no selfcare skills and requires full time care. There were no clinical features suggestive of FVSD. There is a strong maternal family history of epilepsy and possibly educational sub-normality. This patient has two similarly affected brothers who were not exposed to VPA *in utero*, as maternal medication had been changed further to the birth of her eldest son and the recognition of his developmental problems. Obviously, a diagnosis of non-specific X-linked mental retardation is much more likely in this situation, although no identifiable mutation came to light on whole exome screening.

Case 4 is a now twelve-year-old girl with a history of microcephaly, developmental delay and autistic spectrum disorder. She was non-dysmorphic clinically. Extensive paediatric neurological examination and assessment previously undertaken had been supported by a normal MRI brain scan, normal microarray investigations of the chromosomes and detailed, ultimately negative, investigation for myasthenia gravis after ptosis had developed at age 4 years. Whole Exome Sequencing established a *de novo* mutation within the *BRSK2* gene in a highly conserved acceptor splice site. Mutations at this locus are known to cause developmental delay, microcephaly, speech delay, attention deficit and autistic spectrum disorders. A diagnosis of developmental delay consequent on *BRSK2* mutation was returned.

Case 5 is a now fifteen-year-old girl born with metopic suture synostosis and who underwent cranial reconstructive surgery at age two years. She had progressed through mainstream school, but Educational Psychology assessment showed significant deficit in social skills and she was classified as having autistic spectrum disorder. Her facial findings were not strongly suggestive of FVSD, other than for small palpebral fissures. However, her left thumb was notably abnormal with absence of the interphalangeal crease and hypoplasia of the thenar eminence relative to the contralateral side (Figure 4). The combined clinical features of metopic synostosis and thumb abnormalities clearly signalled the diagnosis of FVSD.

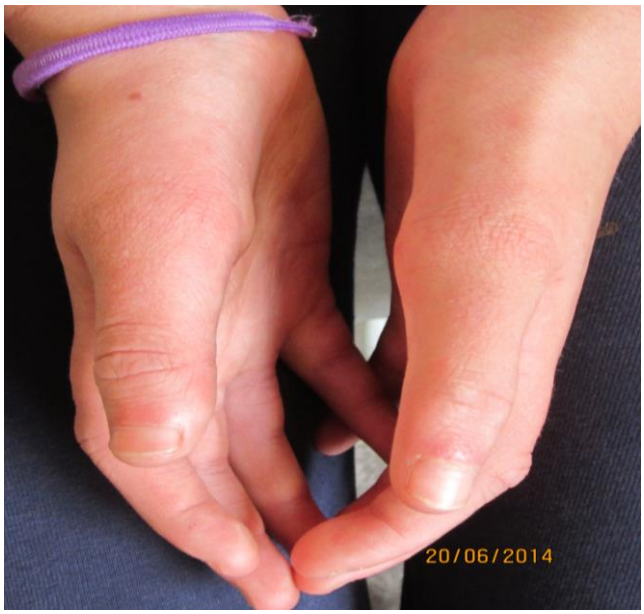

Figure 4.

Table 1: *Data of 6 patients in whom a likely genetic basis of developmental delay was established, notwithstanding VPA exposure in pregnancy.*

Patient	**Array**	**WES**
Male	*De novo* Xq dup 3Mb	Negative
Male	Xp dup 1.7Mb (mat)	Negative
Female	15q13.2 2.1Mb dup *De novo*	Negative
Male	Normal	*SCAG1 gene* Pathogenic intragenic deletion
Female	Normal	*BRSK2 gene* Splice-site pathogenic mutation
Male	Normal	*PURA gene* *De novo* missense mutation

Discussion

Although the condition of FVSD has been known for over twenty-five years, establishing the diagnosis can be demanding. Obviously, some cases pose less diagnostic challenge than others. For instance, the known association with trigonocephaly [17] considerably eases the diagnosis in a case presenting with metopic suture synostosis, even when the facial features may be unconvincing to the experienced eye (Case 5). However, as the illustrative cases show, an open mind as to underlying diagnosis is essential if sensible diagnostic conclusions are to be reached in individual cases.

Clayton-Smith et al., published revised diagnostic criteria in 2019 [16]. An interesting development accepted by this Expert Group is that typical facial features are no longer an absolute requirement to reach the diagnosis of FVSD, whereas this had historically been considered essential to the diagnosis. The essential elements of concluding a diagnosis of Fetal Valproate Spectrum Disorder under the revised criteria now involve;

1. Confirmed exposure to VPA in pregnancy,
2. No recognisable diagnosis to account for the phenotype,
3. Normal microarray and Fragile X syndrome studies,
4. Other teratogenic disorders with overlapping clinical phenotype are excluded in particular Fetal Alcohol Syndrome [18].

Additionally, suggestive features of facial dysmorphic findings, spina bifida, congenital cardiac defects, laryngomalacia, metopic suture synostosis and a joint laxity score of Beighton 6/9 or more are recognised.

Social communication disorders/autistic spectrum diagnosis is recognised to occur in perhaps 6-15% of all cases of FVSD. In our experience, this group of patients presented the most significant diagnostic challenge. Several patients were seen in whom a history of VPA ingestion was considered by parents, and sometimes by their doctors, as causal of their later diagnosis of autistic spectrum disorders, even in the absence of malformations or dysmorphic features which might generally be expected to attend FVSD cases. Even with the revised diagnostic criteria [16] which accept that facial features are not essential to the diagnosis, it is impossible to return a diagnosis of FVSD to patients whose sole neurological finding is autism or variants thereof. Several parents of patients presented for the assessment found this hard to accept and indeed rejected the findings in some instances. However, familial autism studies show that a genetic basis to autism is now a well-established, peer-review published and widely accepted phenomenon. Multiple genetic determinants of familial autism are identified, including rare *de novo* single gene changes, copy number variants, single nucleotide variants and autism spectrum disorder is also confounded by variable penetrance and pleiotropy[19]. For this reason, although unpalatable to carers and parents, some cases in whom autism is the predominant clinical finding cannot be considered to satisfy diagnostic thresholds.

In some instances, the clinical examination clearly identifies the syndrome solely on the basis of the dysmorphic findings. In other instances, with less clear-cut dysmorphic findings, a history of the neonatal period can be especially enlightening, especially of enquiry is specifically made for laryngomalacia [20] or congenital heart disease [5]. In further cases the true cause of the developmental delay has emerged from the absence of typical clinical findings but from the interpretation of the family history, while other patients have been shown to have genetically independent findings, both chromosomal and single gene in nature, which offer adequate and likely explanation for the clinical presentation, according to current guidelines of variant classification[21].

The recent consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability has recommended the new guidelines both for the diagnosis and management of children with Fetal Valproate Spectrum Disorder (FVSD), incorporating new diagnostic criteria [16]. The term FVSD includes all the cases from major congenital malformation to neurodevelopmental delays. The term is used in a similar way as fetal alcohol spectrum disorder[18]. Despite using the FVSD term, it remains difficult to diagnose this condition due to the non-availability of any specific diagnostic test or biomarker.

The new revised diagnostic criteria include the essential, suggestive and supportive features. Essential features must be present for the diagnosis of FVSD, Suggestive features are 10% more common in children with FVSD than the general population and supportive features occur in general population but are found more commonly in FVSD, joint laxity of 6/9 or greater being a good example.

Data from public health [15] based on Irish birth data from 1975 to 2015, suggests that 3126 babies were potentially exposed to VPA in-utero in that time period. 873 of these were born between 2000 and 2015. 153-341 may have experienced some form of major congenital malformation from 1975 to 2015, while 1,250 may have experienced some form of neurodevelopmental delay from 1975 to 2015. These data suggest that the group of cases we have seen and report upon may only represent a minority of exposed cases.

All of our confirmed affected children fulfilled the essential criteria for FVSD, with normal microarray and Fragile X and no other diagnostic reason for their developmental difficulties on investigation. They did not have any exposure to any other teratogenic agent resulting in these difficulties. They all had required suggestive and supportive features to diagnose them with FVSD.

Patient Consent:
Received.

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

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