

Unplanned pregnancies and prenatal exposure to sodium valproate

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ABSTRACT

Sodium Valproate (VPA) is a widely used antiepileptic drug with well-documented teratogenic potential. In utero exposure has been associated with a broad spectrum of congenital anomalies involving the central nervous system, cardiovascular system, skeletal structures, and urogenital tract, as well as neurodevelopmental disorders, including autism spectrum disorder. This study reports a case series of three Tunisian patients aged 2 months to 3 years, born from unplanned pregnancies with in utero exposure to VPA prescribed for maternal epilepsy. The aim of this study is to describe the clinical, phenotypic, and developmental features of these patients and to emphasize the importance of preconception counseling in women with epilepsy. VPA was administered as monotherapy in two cases and in combination with carbamazepine in one case, without periconceptional folic acid supplementation. All patients presented with global developmental delay and characteristic craniofacial dysmorphism. Congenital heart defects were identified in two patients. These findings highlight the increased risk of congenital malformations associated with prenatal exposure to VPA, whether used alone or in combination therapy. The observed features are consistent with the established teratogenic profile of VPA reported in both experimental and clinical studies. This underscores the critical importance of preconception counseling and optimized therapeutic management in women with epilepsy. A multidisciplinary approach including obstetricians, neurologists, pediatricians and midwives is essential to reduce fetal morbidity in our clinical setting.

Keywords: Valproic Acid; Pregnancy; Teratogens; Congenital Abnormalities; Fetal Valproate Syndrome; Neurodevelopmental Disorders; Autism Spectrum Disorder

INTRODUCTION

Sodium Valproate (VPA) is a widely prescribed first-line antiepileptic drug for the management of epilepsy [1]. Despite its therapeutic efficacy, prenatal exposure to VPA is associated with a significantly increased risk of congenital malformations, neurocognitive impairment, and autism spectrum disorder (ASD) [2,3].

The teratogenic potential of VPA was first identified in 1982 through a French population-based malformations surveillance program [4]. Since then, multiple studies have reported an increased incidence of major congenital anomalies in exposed infants, including neural tube defects such as myelomeningocele, congenital heart defects, orofacial clefts, hypospadias, and craniosynostosis [4–6]. The overall rate of congenital malformations has been estimated at approximately 9.3% in VPA-exposed pregnancies, compared with 1.1% in unexposed populations [7].

In addition to structural anomalies, accumulating evidence indicates that prenatal exposure to VPA adversely affects postnatal neurodevelopment, leading to cognitive deficits and an increased risk of ASD [8,9]. In response, regulatory agencies, including the U.S. Food and Drug Administration (FDA), have issued warnings emphasizing the need to restrict VPA use in women of childbearing potential.

Despite these recommendations, VPA continues to be prescribed in pregnant women with epilepsy in Tunisia, and data regarding its impact on child development in this context remain limited.

The aim of this study is to describe the clinical, phenotypic, and developmental characteristics of children prenatally exposed to VPA and to highlight the importance of preconception counseling in women with epilepsy. We report a case series of three children presenting with characteristic facial dysmorphism, congenital malformations—including cardiac defects—and varying degrees of neurodevelopmental delay.

CASE PRESENTATIONS

The main maternal, neonatal, clinical, and paraclinical characteristics of the three patients are summarized in Table 1, allowing comparison of prenatal exposure conditions, phenotypic findings, developmental outcomes, and complementary investigations.

Case 1

A 3-year-8-month-old girl, the first child of non-consanguineous parents, was referred for developmental delay. Her mother, a 30-year-old woman with epilepsy, was treated during pregnancy with sodium valproate (VPA) (1000 mg/day) in combination with carbamazepine (800

mg/day). The pregnancy was unplanned and occurred without folic acid supplementation. Delivery was premature at 34 weeks of gestation. The neonatal period was marked by respiratory distress requiring admission to the neonatal intensive care unit for 20 days. At the age of 3 years, the child presented with global developmental delay, including delayed speech acquisition. Neurological examination revealed a pyramidal syndrome associated with bruxism. Dysmorphic features included hypertelorism and bilateral convergent strabismus. Electroencephalography showed disorganized background activity, whereas brain magnetic resonance imaging was normal. Echocardiography revealed left ventricular hypertrophy with preserved systolic function. Abdominal ultrasound demonstrated hepatic steatosis. Cytogenetic analysis showed a normal karyotype. TORCH serologies and thyroid function tests were normal. Laboratory investigations were unremarkable except for iron-deficiency anemia and mildly elevated lactate dehydrogenase levels.

Case 2

A 1-year-old boy, born to non-consanguineous parents, was prenatally exposed to VPA (1000 mg/day). His 22-year-old mother had poorly monitored epilepsy during pregnancy, without dose adjustment or folic acid supplementation. The child presented with global developmental delay, with inability to sit unsupported at 12 months. On physical examination, growth parameters were within normal limits, with a head circumference of 45.5 cm (-1.5 SD). Neurological examination revealed axial hypotonia. Craniofacial dysmorphism included a prominent forehead, arched eyebrows, hypertelorism, epicanthic folds, broad nasal bridge, rounded nasal tip with anteverted nostrils, long flat philtrum, thin upper lip, and low-set ears (Figure 1).



Figure 1. Facial dysmorphism in patient 2: (A) slightly prominent forehead, arched eyebrows, hypertelorism, epicanthic folds, broad nasal bridge, rounded nose tip with anteverted nostrils, long flat philtrum, thin lips; and (B) low-set ears.

Bilateral clinodactyly of the fifth fingers was also noted. No visceral or skeletal malformations were identified. Cardiac and renal ultrasounds, brain computed tomography, thyroid function tests, and TORCH screening were all normal.

Case 3

A 4-month-old male infant, born at term to non-consanguineous parents, was referred for growth retardation and dysmorphic features. His 25-year-old mother, treated with VPA (1500 mg/day) for epilepsy, had no regular follow-up during pregnancy, with no dose adjustment or folic acid supplementation. The infant presented with hypotrophy (weight: 3.8 kg; -2.7 SD) and microcephaly (head circumference: 34.5 cm; -3.4 SD). Physical examination revealed multiple dysmorphic features, including trigonocephaly, prominent forehead with metopic ridge, arched eyebrows, epicanthic folds, broad nasal bridge, long flat philtrum, thin lips, micrognathia, posteriorly rotated ears, and bilateral convergent strabismus (Figure 2). Echocardiography showed multiple atrial septal defects associated with right heart dilatation. Head and renal ultrasounds were normal. TORCH serologies were negative.

Across all cases, pregnancies were unplanned and inadequately monitored, with no preconception counseling and absence of folic acid supplementation. Maternal epilepsy follow-up was insufficient, with no adjustment of sodium valproate (VPA) dosage during pregnancy. Birth parameters were only partially available; one patient was born prematurely at 34 weeks of gestation with neonatal respiratory distress requiring intensive care, while another presented with intrauterine growth restriction and microcephaly. These findings reflect a high-risk obstetric context that may have contributed to the observed adverse outcomes.



Figure 2. Facial dysmorphism in patient 3: (A) trigonocephaly, high prominent forehead, metopic ridge, arched eyebrows, epicanthic folds, broad nasal bridge, long flat philtrum, thin lips, micrognathism; and (B) posteriorly rotated ears.

Table 1. Clinical presentation and investigations in the three patients

Variable	Patient 1	Patient 2	Patient 3
Sex / Age	Female, 3 years 8 months	Male, 1 year	Male, 4 months
Maternal age	30 years	22 years	25 years
VPA dosage	1000 mg/day	1000 mg/day	1500 mg/day
Therapy type	Polytherapy (VPA + CBZ)	Monotherapy	Monotherapy
Folic acid supplementation	No	No	No
Pregnancy follow-up	Irregular	Absent	Absent
Gestational age	34 WG (premature)	Term	Term
Birth complications	Neonatal respiratory distress	Not specified	Hypotrophy
Head circumference	Not specified	-1.5 SD	-3.4 SD (microcephaly)
Dysmorphic features	Hypertelorism, bilateral convergent strabismus	Prominent forehead, arched eyebrows, hypertelorism, epicanthic folds, broad nasal bridge, rounded nasal tip with anteverted nostrils, long flat philtrum, thin lips, low-set ears, bilateral fifth-finger clinodactyly	Trigonocephaly, high prominent forehead, metopic ridge, arched eyebrows, epicanthic folds, broad nasal bridge, long flat philtrum, thin lips, micrognathia, posteriorly rotated ears, bilateral convergent strabismus
Neurodevelopment	Pyramidal syndrome, bruxism	Axial hypotonia	Microcephaly
Cardiac malformations	Left ventricular hypertrophy with preserved systolic function	None detected	Multiple atrial septal defects with right heart dilatation
EEG	Sleep EEG: poor architecture	Not reported	Not reported
Brain imaging	Brain MRI: normal	Brain CT: normal	Head ultrasound: normal
Abdominal / renal imaging	Abdominal ultrasound: steatotic liver	Renal ultrasound: normal	Renal ultrasound: normal
Genetic investigations	Standard karyotype: normal	Not reported	Not reported
Infectious work-up	TORCH serologies: negative	TORCH serologies: negative	TORCH serologies: negative
Endocrine work-up	Thyroid function: normal	Thyroid function: normal	Not reported
Other laboratory findings	Iron-deficiency anemia; mildly elevated LDH	No significant abnormalities reported	No significant abnormalities reported

DISCUSSION

Sodium Valproate (VPA), or 2-propylpentanoic acid, has long been used as a broad-spectrum antiepileptic agent and for the management of bipolar disorder, migraine, and neuropathic pain [10–12]. Prenatal exposure—particularly during the first trimester and at high doses—carries a markedly increased risk of congenital malformations compared with other antiepileptic drugs, making the management of epilepsy in pregnancy a persistent therapeutic challenge. A clear dose-response relationship has been established, with daily doses ≥ 1000 mg associated with a 30–50% increase in malformation risk [5,11]. All patients in our series received 1000–1500 mg/day, which may account for the severity of clinical findings. Notably, modified-release formulations or divided dosing do not appear to reduce teratogenicity [13].

The teratogenic mechanisms of VPA are multifactorial and involve oxidative stress, DNA damage, and disruption of embryonic pathways. At higher doses, saturation of β -

oxidation shifts metabolism toward glucuronidation, generating reactive intermediates implicated in fetal toxicity [5]. Neural tube defects remain among the most frequently reported anomalies, with an estimated 1–2% risk of spina bifida following first-trimester exposure [14,15]. Folic acid supplementation is therefore recommended for both prevention and neuroprotection, although no neural tube defects were identified in our series despite the absence of supplementation.

Beyond neural tube defects, a wide range of anomalies has been described with prenatal VPA exposure. In a cohort of 403 exposed pregnancies, congenital malformations occurred in 11.1% of infants, with additional fetal losses due to major anomalies identified on ultrasound [5]. Reported defects span the central nervous system, craniofacial structures, the heart, limbs, and urogenital tract. In our patients, no major structural neurological or skeletal anomalies were detected, aside from isolated pyramidal signs, bruxism, and bilateral clinodactyly. Experimental

studies highlight dose-dependent skeletal involvement in animal models [16], and rare upper-limb defects have been reported in humans [6,17].

All three patients exhibited craniofacial dysmorphism consistent with fetal valproate syndrome, including hypertelorism and, in one case, a severe phenotype with microcephaly, trigonocephaly, and metopic ridge, as previously described by Ardinger et al. [18]. Ocular abnormalities such as strabismus, observed in two patients, are also frequently reported, with myopia identified as the most common ocular manifestation [19].

Cardiac malformations occur more frequently in VPA-exposed pregnancies than in those exposed to other antiepileptic drugs [20]. Described anomalies include septal defects, ductus arteriosus, aortic coarctation, pulmonary stenosis, and variant pulmonary artery origins [20–23]. In our series, one patient showed left ventricular hypertrophy with preserved systolic function, and another had multiple atrial septal defects with right-sided dilation, consistent with known VPA-associated cardiac risks.

Neurodevelopmental consequences of prenatal VPA exposure include developmental delay, cognitive impairment, and a substantially increased risk of autism spectrum disorder (ASD) [1,24,25]. Estimated ASD risk is 8–18 times higher than in unexposed populations [1,9]. These findings align with experimental models, such as zebrafish studies demonstrating VPA-induced behavioral and developmental abnormalities [26]. Exposed children also show lower IQ scores by age three [7,27] and poorer academic performance later in childhood [28]. All patients in our series exhibited psychomotor delay; however, the two youngest patients could not be reliably assessed for ASD, and neurological impairment limited cognitive evaluation in the third. These deficits are more likely attributable to VPA than carbamazepine, which has not been consistently associated with adverse cognitive outcomes [29].

Although alternative etiologies such as TORCH infections, thyroid dysfunction, and chromosomal abnormalities were excluded when possible, genetic investigations were limited by the historical context of these cases. Absence of array CGH or next-generation sequencing means that rare syndromes or microdeletions cannot be fully ruled out. Nevertheless, the consistent history of prenatal VPA exposure, characteristic dysmorphic features, and homogeneous clinical pattern strongly support a causal association.

Our findings reinforce well-established evidence while providing contextual data from Tunisia, where important gaps persist in the management of epilepsy during pregnancy, including absent preconception counseling, inadequate follow-up, limited prenatal screening, and the lack of a national congenital malformation surveillance system. As in international registries such as EURAP and NEAD, our patients exhibited variable phenotypic expression despite similar exposure profiles [30,31].

Based on recent evidence, regulatory agencies now impose stricter limitations on VPA use during pregnancy. The FDA contraindicates VPA for migraine prophylaxis and advises restricting its use for epilepsy or bipolar disorder during pregnancy to situations where no safer alternative exists [32]. In Europe, the EMA has implemented a Pregnancy Prevention Programme requiring informed consent and effective contraception for women of childbearing potential [33].

In this context, our case series underscores the urgent need to improve epilepsy care during pregnancy in Tunisia. Strengthening preconception counseling, ensuring appropriate follow-up, and enhancing clinician–patient communication regarding VPA-related risks are essential. Establishing a national congenital malformation surveillance program would further support prevention strategies and improve maternal and child health outcomes.

Conflict of interest: none declared.

REFERENCES

1. Bromley RL, Mawer GE, Briggs M, Cheyne C, Clayton-Smith J, Garcia-Fiñana M, et al. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J Neurol Neurosurg Psychiatry*. 2013 Jun 1;84(6):637–43.
2. Shona SI, Rizk AA, El Sadik AO, Emam HY, Ali EN. Effect of valproic acid administration during pregnancy on postnatal development of cerebellar cortex and the possible protective role of folic acid. *Folia Morphol*. 2018;77(2):201–209.
3. Vajda F. Dose issues in antiepileptic therapy. *J Clin Neurosci*. 2012;19(11):1475–7.
4. Robert E, Guibaud P. Maternal valproic acid and congenital neural tube defects. *Lancet*. 1982 Oct;320(8304):937.
5. Vajda FJ, O'Brien TJ, Hitchcock A, Graham J, Cook M, Lander C, et al. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. *J Clin Neurosci*. 2004 Nov;11(8):854–8.
6. Stadelmaier R, Nasri H, Deutsch CK, Bauman M, Hunt A, Stodgell Ch, et al. Exposure to sodium valproate during pregnancy: facial features and signs of autism. *Birth Defects Res*. 2017 Aug 15;109(14):1134–43.
7. Hernández-Díaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, Holmes LB; North American AED Pregnancy Registry. Comparative safety of antiepileptic drugs during pregnancy. *Neurology*. 2012 May 22;78(21):1692–9.
8. Tomson T. Is valproate contraindicated in young women with epilepsy? YES. *Epileptology*. 2013 Mar;1(1):25–7.
9. Zimmerman R, Patel R, Smith A, Pasos J, Kulesza RJ. Repeated prenatal exposure to valproic acid results in auditory brainstem hypoplasia and reduced calcium binding protein immunolabeling. *Neuroscience*. 2018 May;377:53–68.
10. Löscher W. Valproate: a reappraisal of its pharmacodynamic properties and mechanisms of action. *Prog Neurobiol*. 1999 May 1;58(1):31–59.
11. Nicolini Ch, Fahnestock M. The valproic acid-induced rodent model of autism. *Exp Neurol*. 2018 Jan;299:217–27.
12. Johannessen CU, Johannessen SI. Valproate: past, present, and future. *CNS Drug Rev*. 2003;9(2):199–216.
13. Mawhinney E, Campbell J, Craig J, Russell A, Smithson W, Parsons L, et al. Valproate and the risk for congenital malformations: is formulation and dosage regime important? *Seizure*. 2012 Apr;21(3):215–8.

14. O'Brien TJ, Vajda FJ. Contemporary management of epilepsy in pregnancy. *Aust N Z J Obstet Gynaecol*. 2000 Nov;40(4):413-5.
15. Nau H. Valproic acid-induced neural tube defects. *Ciba Found Symp*. 1994;181:144-52; discussion 152-160.
16. Menegola E, Broccia ML, Di Renzo F, Giavini E. Comparative study of sodium valproate-induced skeletal malformations using single or double staining methods. *Reprod Toxicol*. 2002 Nov;16(6):815-23.
17. Chabrolle JP, Bensouda B, Bruel H, Simon A, Poinot J, Ickowicz V, et al. La craniosténose de la métopique, effet probable de l'exposition intra-utérine à un traitement maternel par le valproate. *Arch Pédiatr*. 2001 Dec;8(12):1333-36.
18. Ardinger HH, Atkin JF, Blackston RD, Elsas LJ, Clarren SK, Livingstone S, et al. Verification of the fetal valproate syndrome phenotype. *Am J Med Genet*. 1988 Jan;29(1):171-85.
19. Glover SJ, Quinn AG, Barter Ph, Moore SJ, Dean JCS, et al. Ophthalmic findings in fetal anticonvulsant syndrome(s). *Ophthalmology*. 2002 May;109(5):942-47.
20. Thomas SV, Ajaykumar B, Sindhu K, Francis E, Namboodiri N, Sivasankaran S, et al. Cardiac malformations are increased in infants of mothers with epilepsy. *Pediatr Cardiol*. 2008 May;29(3):604-8.
21. Mo CN, Ladusans EJ. Anomalous right pulmonary artery origins in association with the fetal valproate syndrome. *J Med Genet*. 1999 Jan;36(1):83-4.
22. Sodhi P, Poddar B, Parmar V. Fatal cardiac malformation in fetal valproate syndrome. *Indian J Pediatr*. 2001 Oct;68(10):989-90.
23. Ten Berg K, van Oppen ACC, Nikkels PGJ, Gittenberger-de Groot AC, van der Voet GB, Brilstra EH, et al. Complex cardiac defect with hypoplastic right ventricle in a fetus with valproate exposure. *Prenat Diagn*. 2005 Feb;25(2):156-8.
24. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L, et al. Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia*. 2010 Oct;51(10):2058-65.
25. Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child*. 2011 Jul;96(7):643-7.
26. Chen J, Lei L, Tian L, Hou F, Roper C, Ge X, et al. Developmental and behavioral alterations in zebrafish embryonically exposed to valproic acid (VPA): an aquatic model for autism. *Neurotoxicol Teratol*. 2018 Mar-Apr;66:8-16.
27. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med*. 2009 Apr 16;360(16):1597-605.
28. Elkjær LS, Bech BH, Sun Y, Laursen TM, Christensen J. Association between prenatal valproate exposure and performance on standardized language and mathematics tests in school-aged children. *JAMA Neurol*. 2018 Jun 1;75(6):663-671.
29. Gaily E, Kantola-Sorsa E, Hiilesmaa V, Isoaho M, Matila R, Kotila M, et al. Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology*. 2004 Jan 13;62(1):28-32.
30. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, Perucca E, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol*. 2011;10(7):609-17.
31. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013;12(3):244-52.
32. U.S. Food and Drug Administration. FDA Drug Safety Communication: Valproate anti-seizure products contraindicated for migraine prevention in pregnant women due to decreased IQ scores in exposed children. 2013.
33. European Medicines Agency. PRAC recommends new measures to avoid valproate exposure in pregnancy. 2018.