Received: 23 September 2021 | Accepted: 12 November 2021

DOI: 10.1002/bdr2.1967

Birth Defects Research | Society for Birth Defects Research & Prevention | WILEY

SHORT COMMUNICATION

Transgenerational adverse effects of valproate? A patient report from 90 affected families

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Abstract

Background: Valproate use during pregnancy increases risk in malformations and neurodevelopmental disorders. Data from the experimental setting in mice showed valproate is a direct inhibitor of histone deacetylase, inducing histone hyperacetylation, histone methylation, and DNA demethylation causing congenital malformations with an epigenetic inheritance. We investigated potential transgenerational adverse effects of valproate.

Methods: We questioned 108 individuals (from 90 families) suffering complications due to valproate exposure in utero who were parents themselves (85 women and 23 men) about the occurrence of malformations and neurodevelopmental disorders in their children. All were member of Aide aux Parents d'Enfants souffrants du Syndrome de l'AntiConvulsivant (APESAC), a charity created in 2011 to provide personal assistance and support to families suffering complications due to valproate exposure during pregnancy.

Results: Among their 187 children they reported 43 (23%) children with malformation(s) (26 hand or foot malformations; 15 dysmorphic facial features; 10 renal/urologic malformations; 6 spina bifida; 4 cardiac malformation; 2 craniosynostosis; 2 cleft lip and palate) and 82 (44%) children with neurodevelopmental disorders (63 problematic behaviors and autism; 41 psychomotor disorders; 16 language problems; 16 attention deficit; 5 mental retardation). Only 88 (47%) children had neither malformation nor developmental disorders.

Conclusion: These data add to the need for funding pharmacoepidemiological investigations of epigenetic inheritance caused by drugs causing malformations or neurodevelopmental disorders. Individuals exposed in utero to valproate must be informed about the risk, so they can consider fertility options, antenatal diagnosis, and adequate early surveillance.

KEYWORDS

drug safety, epigenetic, epilepsy, neurodevelopmental disorders, teratogenicity

1 | INTRODUCTION

Valproate use during pregnancy increases risk in malformations (absolute risk 10.9% vs. 2.5% in offspring of women without epilepsy) and neurodevelopmental disorders (e.g., adjusted hazard ratio for childhood autism 5.2) (Bromley, Weston, & Marson, 2017; Christensen et al., 2013). The documentation of a transgenerational inheritance of neurodevelopmental disorders in mice a decade ago has not yet led to pharmacoepidemiological studies (Tung & Winn, 2010). We aimed to investigate potential transgenerational adverse effects of valproate.

2 | METHODS

Aide aux Parents d'Enfants souffrants du Syndrome de l'AntiConvulsivant (APESAC)'s 2,247 families of mothers having at least one child (F1) who suffered complications due to valproate exposure in utero, in few cases associated with other antiepileptic drugs, were questioned about the occurrence of malformations and neurodevelopmental disorders in next generation children (F2) of parents suffering complications due to valproate exposure (F1). APESAC « Aide aux Parents d'Enfants souffrants du Syndrome de l'AntiConvulsivant » ("Helping Parents of Children Suffering from Anti-Convulsant Syndrome) is a charity created in 2011 by one of us (MM). APESAC nurtures a dedicated and active community and has been collecting information to provide personal assistance and support since 2011.

Formal data collection took place between August 2017 and April 2020. Responses were expanded by phone interviews as needed.

3 | RESULTS

Among 4,436 individuals who suffered complications due to valproate exposure in utero we identified 90 families with at least one child (F1) suffering complications due to valproate exposure in utero who was a parent themselves. Sadly, as action was slow following the earliest warnings of teratogenicity first published in 1982 in *The Lancet*, some mothers had several children exposed. There were 108 individuals (F1) suffering complications due to valproate exposure in utero who were parents themselves: 85 women and 23 men, born between 1971 and 1999. Table 1 describes the malformations and neurodevelopmental disorders reported among their 187 children (F2): 43 (23%) have malformation(s) and 82 (44%) have developmental disorder(s). Only 88 (47%) of children (F2) had neither malformation nor developmental disorders.

4 | DISCUSSION

Our results are compatible with a transgenerational effect of the initial teratogen, supported by previous experimental research: (a) valproate is a direct inhibitor of histone deacetylase, inducing histone hyperacetylation, histone methylation, and DNA demethylation. These epigenetic modifications during early mouse organogenesis cause congenital malformations (Tung & Winn, 2010); (b) in mice autism spectrum disorders induced by valproate can be epigenetically transmitted, at least to the third generation (Choi et al., 2016; Tartaglione et al., 2019).

Further, the adverse outcomes both from F1 mothers and F1 fathers align with observations in mice showing the induction of differential histone retention sites in round spermatids and later stages which can be transmitted to subsequent generations through epigenetic transgenerational inheritance (Ben Maamar, Beck, Nilsson, McCarrey, & Skinner, 2020). The very low rate of parenthood (2.4%) among F1 individuals exposed in utero to valproate may have several explanations: (a) major malformations and/or neurodevelopmental disorders are hardly compatible with sexual activity and parenthood;

TABLE 1 Prevalence of at least a malformation or a developmental disorder in the 187 children (F2) from 108 individuals (F1) exposed in utero to valproate with adverse outcomes

Disorder	149 F2 children (from 85 F1 women)	38 F2 children (from 23 F1 men)	Total 187 F2 children (from 108 F1 parents)
Malformations (a) alone: *n* (%)	14 (9%)	3 (8%)	17 (9%)
Developmental disorders (b) alone: *n* (%)	47 (32%)	9 (24%)	56 (30%)
Both (a) and (b): *n* (%)	24 (16%)	2 (5%)	26 (14%)
None: *n* (%)	64 (43%)	24 (63%)	88 (47%)

Note: (a) Hand or foot malformations (n = 26); dysmorphic facial features ($n = 15$); renal/urologic malformations ($n = 10$); spina bifida ($n = 6$); cardiac malformation ($n = 4$); craniosynostosis ($n = 2$); cleft lip and palate ($n = 2$). (b) Problematic behaviors and autism ($n = 63$); psychomotor disorders ($n = 41$); language problems ($n = 16$); attention deficit ($n = 26$); mental retardation ($n = 5$).

(b) many are still young; and (c) some may chose childlessness in light of their own and parents' experience. However, the question of whether valproate affects fertility itself deserves further research.

5 | LIMITATIONS

As this series describes F1 individuals with serious adverse effects related to valproate exposure we cannot comment on the risk to the offspring of F1 individuals exposed to valproate without serious adverse effects.

Being a charity aimed at providing support to families, we regretted we could not formally corroborate reported malformations and medical diagnoses with medical records nor whether F2 children's neurodevelopmental diagnoses were professionally confirmed. Since November 2017, the charity made serial formal requests to the Ministry of Health for funding medical research to investigate possible transgenerational adverse effects of valproate, they have been turned down.

However, (a) the reported malformations can only have followed a medical diagnosis and even if hand:foot malformations ($n = 26$) were excluded from the numbers of affects, the prevalence of major undeniable malformations is still a "red flag" with renal/urologic malformations ($n = 10$); spina bifida ($n = 6$); cardiac malformation ($n = 4$); craniosynostosis ($n = 2$); cleft lip and palate ($n = 2$); (b) parents only reported neurodevelopmental disorders that open access to special education programs. It is possible that some families have unrecognized inherited congenital chromosomal abnormalities associated with the parental exposure to antiepileptic, but it is unlikely that the commoner ones (e.g., Fragile X) could have been overlooked by health professionals caring for individuals whose family has several members affected.

6 | CONCLUSION

We call for the funding of an international consortium for pharmacoepidemiological investigation of epigenetic inheritance caused by drugs. It is not acceptable that a decade's worth of experimental findings about epigenetic inheritance has not raised alarms about the transgenerational effects of drugs or other toxic chemical products causing malformation or neurodevelopmental disorders (Tung & Winn, 2010; Choi et al., 2016). Meanwhile, all F1 individuals exposed in utero to valproate must be informed about the risk, so they can consider their fertility options, antenatal diagnosis, and adequate early surveillance.

CONFLICT OF INTEREST

Marine Martin created a charity in 2011 « Aide aux Parents d'Enfants souffrants du Syndrome de l'AntiConvulsivant » (APESAC https://www.apesac.org/) ("Helping Parents of Children Suffering from Anti-Convulsant Syndrome) and initiated lawsuits.

ETHICS STATEMENT

Not required. The interviews were performed according to the French Data Protection Act (Ref. MR-001 Règlement Général sur la Protection des Données) and registered by the National Commission for Informatics and Freedoms (CNIL): #2067661 on April 26, 2017.

AUTHORS CONTRIBUTION

Marine Martin designed the data collection instruments and collected data. Catherine Hill carried out the initial analyses. Catherine Hill and Alain Braillon drafted the initial manuscript. Marine Martin, Catherine Hill, Susan Bewley, Alastair H. MacLennanand Alain Braillon contributed to the interpretation of data, reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Martin, M., Hill, C., Bewley, S., MacLennan, A. H., & Braillon, A. (2021). Transgenerational adverse effects of valproate? A patient report from 90 affected families. *Birth Defects Research*, 1–4. https://doi.org/10.1002/bdr2.1967