Transgenerational neurodevelopmental disorders from prenatal valproate exposure?

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Abstract

Background: Multiple substances (e.g. medicines, environmental chemicals) can experimentally induce epigenetic changes that increase risks of major psychiatric conditions. Transgenerational effects from prenatal valproate exposure have been evidenced in an experimental model. Among 187 children from 108 individuals suffering complications due to valproate exposure in utero who were parents themselves, malformations were observed in 43 and neurodevelopmental disorders in 82, only 88 (47) had neither malformation nor developmental disorders.

Methods: This observational study compared risks in children of siblings who were exposed in utero to valproate and in children of unexposed siblings, based on family-reported data.

Results: Among 20 parents exposed in utero to valproate alone (n=17) or associated with another anti-epileptic drug (n=3), three had no related harms, nine had neurodevelopmental disorders, three had malformations, and five had both. The 40 children of these exposed parents were 2.9 times more likely to have a neurodevelopmental disorder or malformation than their 40 first cousins. Risks were similar regardless of whether the parent exposed in utero had a neurodevelopmental disorder or not.

Discussion: The 3.6-fold increased risk of neurodevelopmental disorders in children of parents exposed in utero to valproate, compared to first cousins, cannot easily be explained by confounding.

Conclusion: Individuals exposed in utero to valproate should be informed of possible transgenerational effects to allow informed reproductive choices, antenatal diagnosis, and early surveillance of their children.

Neurodevelopmental disorders after prenatal exposure to sodium valproate were first documented in 1984**,** two years after malformations had been reported.(1) Since the early 2000s, prenatal valproate exposure has served as an experimental model for autistic behaviors in animals, and transgenerational effects were documented a decade ago in mice.(2) A clinical report observed a high rate of malformations and neurodevelopmental disorders (23% and 44%, respectively) among 187 children born to 108 individuals affected by valproate exposure in utero.(3) Only 88 (47%) children had neither malformation nor developmental disorders.

Methods

We compared malformations and neurodevelopmental disorders in children of siblings either exposed or not exposed in utero to valproate. Families were identified from the database of the Association to Help Parents of Children Suffering from Anti-Convulsant Syndrome (APESAC), which includes 4,095 families. All 17 families with at least one parent exposed in utero to valproate and one unexposed sibling—both of whom had children—were studied. Data were collected between August 2017 and March 2025.

Results

The proportions of children with neurodevelopmental disorders or malformations in the two groups (defined by parental exposure) were compared using a stratified 2×2 analysis, with an exact Cochran–Mantel–Haenszel test and a permutation test. The common relative risk was estimated using the Mantel–Haenszel estimator.

Among 20 parents exposed in utero to valproate (17 to valproate alone, 3 with another antiepileptic), three had no related harms, nine had neurodevelopmental disorders, three had a malformation, and five had both. The 40 children of exposed parents were 2.9 times (95% CI 1.5–5.8) more likely to have a neurodevelopmental disorder or malformation than their 40 first cousins ($p<0.0009$, exact permutation test stratified by family; see Table 1).

Table 1. Neurodevelopmental disorders (NDD) or malformations (Malf.) in children from siblings with and without in-utero exposure to valproate.

Family	Parents exposed in utero to	Cases: children of exposed parents	Parents without valproate	Control

	valproate (n, sex)				exposure in utero (n,sex)	
		Affected/total (n)	Neurodevelopmental disorder (n)	Malformation (n)		Affected/total (n)
A	1w, 2 m	2/4	1P 1L	0	1w	0/1
B	1w	2/2	2 ACLT	0	3w	1/6
C	1w	0/2	0	0	1w	0/2
D	1w	1/1	1LR	0	2w	0/2
E	1m	1/3	1C	0	1m	0/2
F	1w	1/1	1CLT	1M*	1m	0/1
G	1w	1/2	1I	0	1m	0/2
H	1m	2/2	1ALPT 1A	0	1w	0/1
I	1w	1/1	1C	0	1w	1/1
J	1w	0/2	0	0	1w	0/2
K	1w	3/3	1CILPT 1CL 1L	1U* 1G*	1m	1/2
L	1w	1/1	1C	0	1w	0/1
M	1w	3/6	1ACILT 1CIL 1CI	0	1m	0/2
N	1m	2/2	1CI 1C	0	1w	2/4
O	1w	0/1	0	0	2w	**2**/5
P	1w	2/2	1C 1I	1U*	1w	0/3
Q	1w, 1m	1/5	1C	0	1w	2/3
Total	14w, 6m	23/40	23	4	16w, 5m	9/40

* Association with at least one neurodevelopmental disorder
m= man; w=woman
A: Learning disability (5 vs 2); C: Behavioral disorder/autism (15 vs 2); I: Social interaction disorder (7 vs 0); L: Language disorder (11 vs 2); P: Psychomotor disorder (3 vs 1); R: Mental retardation (1 vs 1); T: attention deficit hyperactivity disorder (6 vs 2)
G: Congenital cardiopathy; M: Limb malformation (club foot); O: Cleft lip and palate; U: Kidney/urogenital malformation; Z: Unspecified malformation.

Neurodevelopmental disorders were more frequent in exposed children than in controls: behavioral disorder/autism (15 vs 2), language disorder (11 vs 2), social interaction disorder (7 vs 0), attention deficit hyperactivity disorder (6 vs 2), learning disability (5 vs 2), psychomotor disorder (3 vs 1), and intellectual disability (1 vs 1) (Table 1). The overall risk was 3.6 times higher (95% CI 1.7–7.6) in children of exposed parents than in children of unexposed siblings ($p<0.0001$).

Four exposed children with neurodevelopmental disorders also had malformations (cardiac, limb, hypospadias, urogenital), versus four controls (cardiac, cleft lip/palate, limb, unspecified). Although not formally assessed, exposed parents appeared more likely than their unexposed siblings to have neurodevelopmental disorders. However, among the 11 children of exposed parents without neurodevelopmental disorders (3 parents had malformations), 6 developed disorders.

Discussion

Children of both men and women exposed to valproate in utero appear to have a high risk of neurodevelopmental disorders. The 3.6-fold excess risk compared with first cousins raises the question of why such a strong signal has been overlooked. Mechanisms remain speculative, valproate is known to inhibit histone deacetylases, potentially inducing heritable epigenetic changes.

The population studied is small. Few women used antiepileptic drugs during only some pregnancies, and restricting to families in which both exposed and unexposed siblings had children further reduced the sample. The small number of malformations limits conclusions for this outcome. Co-exposures to other antiepileptic drugs were not investigated.

APESAC families may represent more severe cases, but risks were similar whether exposed parents themselves had neurodevelopmental disorders or not (17/29 vs 6/11). Limitations include reliance on family-reported data and professional diagnoses not independently verified. However, diagnoses were supported by institutional care for special needs, and participants were contacted individually. Age at diagnosis was not systematically recorded.

As a charity, APESAC cannot compete for government research funding, and early requests for support were unsuccessful; consequently, detailed confounding data were unavailable. The sibling comparison provides a pragmatic way to reduce confounding by comparing within families, offering an alternative to complex adjustments in heterogeneous populations prone to analytical flexibility.(4)

Conclusion

Although further studies are needed, individuals exposed in utero to valproate should be informed of possible transgenerational effects to support reproductive choices and early surveillance of their children. Early intervention (ages 2–3 years) offers the best chance of long-term benefit.

Various substances (drugs, environmental chemicals, pollutants) can induce epigenetic changes that increase psychiatric risk.(5) The lack of pharmaco-epidemiological investigation of transgenerational psychiatric effects despite accumulating red flags raises concerns that "translational medicine" could be an empty concept when the issue is safety. Pr. Herxheimer, the founder of the Drug and Therapeutics Bulletin, noted that patient reports can be uniquely informative. Why are stakeholders—industry, regulators, academic institutions, and professional organizations—failing to respond adequately to red flags?(2,3) Why were lessons not learned from diethylstilbestrol? Large, well-funded studies with appropriate controls are urgently needed.

Statement of Ethics

Study approval statement: Authorization was granted by the National Commission for Information Technology and Civil Liberties (Commission Nationale de l'Informatique et des Libertés) on June 2, 2017.

Authors Contributions:

Hill and Martin had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Hill and Martin. Acquisition, analysis, or interpretation of data: Hill, Le Teuff and Martin. Drafting of the manuscript: Hill and Martin. Critical review of the manuscript for important intellectual content and validation: Hill, Martin, Le Teuff, Alain Braillon.

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