Current Literature
In Clinical Science

In Utero Valproate Exposure and Autism: Long Suspected, Finally Proven

Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism.

Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, Vestergaard M. *JAMA* 2013;309(16):1696–1703.

IMPORTANCE: Valproate is used for the treatment of epilepsy and other neuropsychological disorders and may be the only treatment option for women of childbearing potential. However, prenatal exposure to valproate may increase the risk of autism. OBJECTIVE: To determine whether prenatal exposure to valproate is associated with an increased risk of autism in offspring. DESIGN, SETTING, AND PARTICIPANTS: Population-based study of all children born alive in Denmark from 1996 to 2006. National registers were used to identify children exposed to valproate during pregnancy and diagnosed with autism spectrum disorders (childhood autism [autistic disorder], Asperger syndrome, atypical autism, and other or unspecified pervasive developmental disorders). We analyzed the risks associated with all autism spectrum disorders as well as childhood autism. Data were analyzed by Cox regression adjusting for potential confounders (maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations, and parity). Children were followed up from birth until the day of autism spectrum disorder diagnosis, death, emigration, or December 31, 2010, whichever came first. MAIN OUTCOMES AND MEASURES: Absolute risk (cumulative incidence) and the hazard ratio (HR) of autism spectrum disorder and childhood autism in children after exposure to valproate in pregnancy. RESULTS: Of 655 615 children born from 1996 through 2006, 5437 were identified with autism spectrum disorder, including 2067 with childhood autism. The mean age of the children at end of follow-up was 8.84 years (range, 4-14; median, 8.85). The estimated absolute risk after 14 years of follow-up was 1.53% (95% CI, 1.47%-1.58%) for autism spectrum disorder and 0.48% (95% CI, 0.46%-0.51%) for childhood autism. Overall, the 508 children exposed to valproate had an absolute risk of 4.42% (95% CI, 2.59%-7.46%) for autism spectrum disorder (adjusted HR, 2.9 [95% CI, 1.7-4.9]) and an absolute risk of 2.50% (95% CI, 1.30%-4.81%) for childhood autism (adjusted HR, 5.2 [95% CI, 2.7-10.0]). When restricting the cohort to the 6584 children born to women with epilepsy, the absolute risk of autism spectrum disorder among 432 children exposed to valproate was 4.15% (95% CI, 2.20%-7.81%) (adjusted HR, 1.7 [95% CI, 0.9-3.2]), and the absolute risk of childhood autism was 2.95% (95% CI, 1.42%-6.11%) (adjusted HR, 2.9 [95% CI, 1.4-6.0]) vs 2.44% (95% CI, 1.88%-3.16%) for autism spectrum disorder and 1.02% (95% CI, 0.70%-1.49%) for childhood autism among 6152 children not exposed to valproate. CONCLUSIONS AND RELEVANCE: Maternal use of valproate during pregnancy was associated with a significantly increased risk of autism spectrum disorder and childhood autism in the offspring, even after adjusting for maternal epilepsy. For women of childbearing potential who use antiepileptic medications, these findings must be balanced against the treatment benefits for women who require valproate for epilepsy control.

Commentary

The cognitive teratogenic activity of valproate (VPA) is crystallizing with the latest report on the association of in utero VPA exposure and the risk of autism determined from a population-based study utilizing Danish national medical databases. Children born between 1996 and 2006 were followed for the documented occurrence of autism up to 14 years of age, with a mean follow-up of 9 years. The astounding results were that for children born to mothers who took VPA during pregnancy, the risk of childhood autism increased 3-fold and the risk of autism spectrum disorder (ASD) increased 5-fold over the general population risk. The authors make the point that the absolute risk to VPA-exposed children remains low at less than 5%, although the upper 95% confidence interval (CI) limit for ASD was 7.49%. There was no contribution of maternal epilepsy to the risk of VPA use.

In contrast to the structural teratogenesis with VPA, which manifests with hypospadias and spina bifida and occurs with first trimester exposure (1), the autism risk was present in this study with VPA exposure starting at any trimester during pregnancy. The first report to show an effect of the timing of antiepileptic drug (AED) exposure during pregnancy on adverse cognitive outcomes was an evaluation of phenobarbital

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exposure (2). A small cohort of adult men exposed in utero had significantly lower verbal IQs (approximately 7 points lower) compared with age-matched unexposed men; exposure during the third trimester compared with first-trimester use increased the risk. None of these mothers used phenobarbital for epilepsy but for anxiety or hypertension. This timing effect was not shown in this recent report with VPA; however, the number of late exposures was "low," as per the investigators.

Another deviation from previous work on structural teratogenesis was that investigators found no dose effect to the risk when dichotomizing the doses to either above 750 mg/d or below. The risk of major congenital malformations with exposure at less than 700 mg/d has been reported as 4%, with successive increases in risk associated with increased dose; major malformation rates are 20% at more than 1,500 mg/d (3).

The autism risk with VPA exposures in this population was unchanged when children with congenital malformations were removed from the analysis; it is not stated whether these were major or minor malformations, and perhaps it would be difficult to determine from the medical databases. Evidence from one report indicates that cognitive deficits do not associate with major congenital malformations in offspring exposed to VPA in utero (4). However, as concluded by Holmes et al. in 2005, the presence of minor malformations such as midface or digital hypoplasia occurring after in utero exposure with carbamazepine, phenytoin, or phenobarbital should prompt an evaluation for developmental delay, as IQ scores of 10 to 12 points below expected were found in children with these minor malformations (5).

How did we come to explore and refine this association between VPA and autism? One intriguing early report by Adab et al. in 2001 (6) indicates an increase in educational needs for school-age children exposed to VPA in utero. This was a questionnaire study of 727 mothers with epilepsy (57% responder rate); 87% of their children were attending mainstream schools and did not have additional educational needs. However, of the remainder of children who needed remedial help in a mainstream school or attended a special school, VPA monotherapy exposure was overrepresented by 3-fold compared with children not exposed to AEDs (odds ratio [OR] 3.4, 95% CI, 1.63–7.10). Carbamazepine exposure was not associated with increased risk.

Two subsequent retrospective studies showed a risk of significantly lower verbal IQs in children exposed in utero to VPA as compared with other AED exposure or to nonexposed children (7, 8). In the most recent report from the NEAD study, in which children born to mothers with epilepsy taking AEDs were evaluated prospectively, VPA exposure was associated with a significantly lower IQ (approximately 7 points lower) compared with carbamazepine, phenytoin, or lamotrigine exposure. AED exposure adversely affected verbal IQ specifically in these studies; however, only a clear dose effect was present for VPA across all cognitive domains (9). In another NEAD study report from 2011, compared with children with other AED exposures, children with VPA exposure were reported by their parents to have difficulty with social skills and adaptive functioning associated with VPA dose, and a higher-than-expected occurrence of hyperactive behaviors, indicating a risk for the development of attention-deficit/hyperactivity disorder (10). Key features of autism are impaired verbal and nonverbal communication, impaired social interaction, and narrow, repetitive, or stereotyped behavior. While autism is not specifically commented upon in these reports, it appears that an autistic clinical picture is forming.

One of the most convincing initial reports on the association between in utero VPA exposure and ASD was put forth by Bromley et al. in 2008 (11). In this prospective study of the offspring of women with epilepsy and an untreated, nonepileptic control group, 6.3% of VPA-exposed children had ASD or key symptoms of ASD including language impairment, reduced attention, and social difficulties compared with 0.9% of the control children, a 7-fold increase in occurrence (11). A long-term follow-up of this cohort, reported recently (12), showed that 6 of 50 (12%) of the VPA-exposed children were diagnosed with neurodevelopmental disorders; five of these were ASD. Therefore, the magnitude of absolute and relative risk of autism with VPA exposure in this study is similar to the population-based report by Christensen et al.

In a recent comprehensive review of both clinical and animal studies on the topic of VPA and autism (13), it appears that rats can be made less sociable and will produce much fewer ultrasonic vocalizations when exposed to VPA in utero, therefore comprising an autistic rat (my favorite kind). Unlike the human data, a very specific timing of vulnerability is present—embryonic day 12. While many causative hypotheses are discussed in this article, including molecular and cellular mechanisms, disruption of cortical development is produced by VPA exposure at this point in fetal development. The effect is to increase local cortical connectivity in multiple cortical areas; this indicates, paradoxically, a decrease in the strength of these connections, and further, the potential for increased excitability of these circuits, which may in turn alter normal behavior. This hypothesis is intriguing for the neurophysiologists among us.

Could VPA teratogenesis lead to answers about the causes of autism? The convergence of these fields may eventually result in turning two very tragic scenarios into scientific work that could prevent one of the most striking neurocognitive challenges of our time.

by Cynthia L. Harden, MD

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