

CORRESPONDENCE



Cognitive Function after Fetal Exposure to Antiepileptic Drugs

TO THE EDITOR: Meador et al. (April 16 issue)¹ suggest that children who had been exposed to valproate in utero had significantly lower IQ scores than those who had been exposed to other antiepileptic drugs. However, the results of their study should be interpreted with caution. Many factors have a role in the neuropsychological development of children, apart from fetal exposure to antiepileptic drugs. We are not given details of the quality of the home environment, which has been recognized as a key environmental influence on child development.² The Home Screening Questionnaire (HSQ) is a widely used tool to assess the qualities of the home environment that may influence the development of children,³ such as emotional and verbal responses of the mother and avoidance of restriction and punishment.

Although the study by Meador and colleagues included detailed monitoring of multiple potential confounding factors relating to child IQ, the HSQ may be helpful for obtaining more detailed and appropriate assessments of and conclusions about the children at the age of 6 years.

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1. Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 2009;360:1597-605.

2. Zhou SJ, Baghurst P, Gibson RA, Makrides M. Home environment, not duration of breast-feeding, predicts intelligence quotient of children at four years. *Nutrition* 2007;23:236-41.

3. Frankenburg WK, Coons CE. Home Screening Questionnaire: its validity in assessing home environment. *J Pediatr* 1986; 108:624-6.

THE AUTHORS REPLY: Liu et al. suggest that the results of our recent study should be interpreted with caution because of the lack of details on the home environment. In fact, we assessed home environment at 1 year of age using the Home Observation for Measurement of the Environment (HOME) scale, an established instrument with good psychometric properties.¹⁻³ HOME results were not included, because most children in the United Kingdom were older than 1 year of age by the time of the merger with the U.S. study. Mean (\pm SD) scores on the HOME scale among the 187 children who underwent this assessment were: carbamazepine, 39.7 \pm 5.3; lamotrigine, 42.1 \pm 2.9; phenytoin, 39.6 \pm 4.2; and valproate, 40.1 \pm 4.0. HOME scale scores have a range of 0 to 45, with a higher score indicating a better home environ-

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ment. When added to the statistical model that includes maternal IQ, drug group, dose, maternal age, gestational age, and folate, the score on the HOME scale was not a significant predictor of child IQ in this subgroup ($P=0.55$). The addition of HOME results (whether analyzed as imputed data for intention-to-treat analyses or completer data only, or categorized according to quartiles) does not change our conclusion about associations between maternal valproate use and childhood IQ.

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1. Bradley RH, Caldwell BM. Home Observation for Measurement of the Environment: a validation study of screening efficiency. *Am J Ment Defic* 1977;81:417-20.
2. Bradley RH, Mundfrom DJ, Whiteside L, Casey PH, Barrett K. A factor analytic study of the infant-toddler and early childhood versions of the HOME Inventory administered to white, black, and Hispanic American parents of children born preterm. *Child Dev* 1994;65:880-8.
3. Bradley RH. The Home Inventory: review and reflections. *Adv Child Dev Behav* 1994;25:241-88.

The EAST Syndrome and *KCNJ10* Mutations

TO THE EDITOR: Bockenbauer et al. (May 7 issue)¹ report on a unique constellation of multiorgan signs and symptoms — epilepsy, ataxia, sensorineural deafness, and a renal salt-losing tubulopathy, which they term the EAST syndrome — associated with the homozygous missense mutations of the *KCNJ10* gene encoding a potassium channel.

In the Discussion section, the authors propose that the seizures in the patients in their study were due to an extracellular accumulation of potassium in the absence of fully functional *KCNJ10*; this accumulation decreased the membrane potential and facilitated further excitations. This explanation is reasonable. However, another possibility — demyelinating disorders of the central nervous system — should not be ignored. *KCNJ10* has been proved to be crucial for oligodendrocyte differentiation and in vivo myelination.² *Kcnj10* knockout mice have dysmyelination, extensive vacuolation, and apoptosis of glial cells, along with axon degeneration.² The occurrence of epileptic seizures is a well-known clinical feature in the demyelination diseases of the central nervous system. Therefore, myelination disorders induced by mutant *KCNJ10* probably account for the seizures in patients with the EAST syndrome as well.

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1. Bockenbauer D, Feather S, Stanescu HC, et al. Epilepsy, ataxia, sensorineural deafness, tubulopathy, and *KCNJ10* mutations. *N Engl J Med* 2009;360:1960-70.
2. Neusch C, Rozengurt N, Jacobs RE, Lester HA, Kofuji P. Kir4.1 potassium channel subunit is crucial for oligodendrocyte development and in vivo myelination. *J Neurosci* 2001;21:5429-38.

THE AUTHORS REPLY: Shi and Zhao emphasize the importance of *KCNJ10* for brain function in the EAST syndrome. Clearly, there are differences between *Kcnj10* in knockout mice and *KCNJ10* in patients with the EAST syndrome; most obviously, in our study, mice died shortly after birth, whereas our patients lived. Similarly, the mice indeed showed extensive myelination defects, but routine brain magnetic resonance imaging in our patients was normal. This finding makes it difficult to ascribe seizures to demyelination. Whether this difference is due to differences between species or to the residual function of mutant *KCNJ10* in preventing demyelination remains to be seen. Sequence variations in *KCNJ10* have been shown to be associated with seizure susceptibility.¹

Involvement of the central and peripheral nervous systems in the EAST syndrome appears to be complex. Studies of nerve-conduction velocity in our patients showed normal findings. Early and severe ataxia makes the assessment of mental involvement difficult. We did not observe obvious mental retardation in some of the patients. All neurologic findings, including hearing impair-