



Editors' Note: Commenting on “Autism and epilepsy: A population-based nationwide cohort study,” Dr. Sethi expresses the difficulty in determining what comes first, the epilepsy or the autism, in children who have both. Sundelin et al., authors of the study, agree that the association may be due to a shared mechanism. There are different factors that come into play, such as cultural differences, genetics, and children’s survival. They suggest a study that compares incidence of autism among individuals with epilepsy in different countries and those of the same ethnicity now living in the United States. In response to “CSF concentrations of 5-methyltetrahydrofolate in a cohort of young children with autism,” Dr. Barrett questions the definition of low 5-methyltetrahydrofolate (5-MTHF) in the study and points out different results with different normative data. Dr. Shoffner, an author of the study, explains that they assessed CSF 5-MTHF over time. The latter varied significantly but was not associated with any measures of adaptive behavior, cognitive ability, or autism spectrum disorder symptom severity.

—*Chafic Karam, MD, and Robert C. Griggs, MD*

**LETTER RE: CSF CONCENTRATIONS OF
5-METHYLTETRAHYDROFOLATE IN A COHORT
OF YOUNG CHILDREN WITH AUTISM**

Geraldine Barrett, London: Shoffner et al.¹ reported that “a correlation between CSF 5-MTHF

(5-methyltetrahydrofolate) and serum folate was not observed.⁷ This finding contrasts previous studies of children where a positive correlation was found.^{2,3} Further, the previous studies estimated the ratio of CSF to serum folate to be about 3,^{2,3} which is in contrast to the much lower ratio (approximately 1) found by the authors.¹

Shoffner et al. defined low CSF folate as <40 nmol/L and based all analyses around this cutpoint. The difficulty with this approach is that CSF folate is a continuous measure and the cutpoint currently has little supporting research evidence. For instance, if the value of 72 nmol/L (the lower value for children aged 5–10 given by Aylett et al.⁴) were applied to figure 1,¹ it could be concluded that most children had low CSF folate at both visit 1 and visit 2.

Considerable research is still needed on this topic. What is most important: the absolute value of CSF folate, the ratio of CSF to serum folate, or both? How do these relate to neurologic symptoms? Ultimately, who will benefit from folinate (a relatively safe and inexpensive therapy)?

1. Shoffner J, Trommer B, Thurm A, et al. CSF concentrations of 5-methyltetrahydrofolate in a cohort of young children with autism. *Neurology* 2016;86:2258–2263.
2. Ormazabal A, Garcia-Cazorla A, Perez-Duenas B, et al. Determination of 5-methyltetrahydrofolate in cerebrospinal fluid of paediatric patients: reference values for a paediatric population. *Clin Chim Acta* 2006;371:159–162.
3. Perez-Duenas B, Ormazabal A, Toma C, et al. Cerebral folate deficiency syndromes in childhood: clinical, analytical, and etiologic aspects. *Arch Neurol* 2011;68:615–621.
4. Aylett SB, Neergheen V, Hargreaves IP, et al. Levels of 5-methyltetrahydrofolate and ascorbic acid in cerebrospinal fluid are correlated: implications for the accelerated degradation of folate by reactive oxygen species. *Neurochem Int* 2013;63:750–755.

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