

effect, although additional patients will have to be studied before any firm conclusions can be drawn.

Mahoney et al. suggest that frequency of drug administration may also contribute to ototoxicity. Because each child in our first study received cisplatin at 3-week intervals, we were unable to assess the effect of this variable. A prospective study including larger numbers of patients treated at several different intervals is clearly needed.

We do not believe that our findings, or those of Mahoney et al., should discourage use of cisplatin when it is clearly the drug of choice. We do recommend close audiologic monitoring in children receiving this agent, particularly those who have had prior cranial irradiation.

#### REFERENCE

1. McHaney V, Thibadoux G, Hayes F, Green A: Hearing loss in children receiving cisplatin chemotherapy. *J PEDIATR* 102:314, 1983.

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### Follow-up in a child with 5,10-methylenetetrahydrofolate reductase deficiency

#### To the Editor:

We report the follow-up in a child with 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency.<sup>1</sup> This girl is now 5 years of age (weight 19.5 kg, height 103 cm). She walked at 18 months, and had been doing well until 3 years of age, with good social behavior but with delayed speech; her head circumference was 48.5 cm (40.5 cm at 7 months, before treatment). She was receiving the same treatment, i.e., methionine, folinic acid, pyridoxine, hydroxocobalamin (OH-B12). From time to time she excreted small amounts of homocystine in urine, related to omissions of treatment. At 33 months of age, we made a trial with 5-methyltetrahydrofolate 5 mg orally twice a day, with OH-B12 0.5 mg per day orally. Homocystinemia did not rise above 13  $\mu\text{mol/L}$  (233  $\mu\text{mol/L}$  before treatment). 5-Methyltetrahydrofolate had to be withdrawn because of its instability, and the previous treatment was resumed. At 3 years of age, the mother stopped all treatment for 2 months. The child became lethargic and hypotonic, with recurrence of homocystinuria 157  $\mu\text{mol/day}$ , which disappeared after treatment was resumed. However, the child's comportment remained somewhat deteriorated. Subsequently, treatment has been stopped several times by the mother, resulting in a progressive worsening in the child's condition. She is now autistic and hyperactive, but without abnormal neurologic signs (head circumference 49 cm). CT scan of the brain and EEG findings are normal, as are results of electrophysiologic studies of peripheral nerves. There is no lens dislocation. While at home,

because of bad compliance with treatment, she had homocystinemia 5 to 13  $\mu\text{mol/L}$ , homocystinuria 46 to 61  $\mu\text{mol/day}$ , hypomethioninemia 0 to 10  $\mu\text{mol/L}$ , low serum folate level (*Lactobacillus casei*) 2.3 ng/ml (normal 5 to 15 ng/ml) and red cell folate 95 ng/ml (normal >250), and low serum free carnitine 25.5  $\mu\text{mol/L}$  (normal  $50 \pm 10 \mu\text{mol/L}$ ). When hospitalized and receiving her treatment, all values were normal except for a decreased CSF (9.7 ng/ml) to serum (7 ng/ml) folate ratio of 1.38:1 (normal 3:1). Without treatment, the CSF value for 5-HIAA was 32 ng/ml (normal for age  $40 \pm 5$  (ng/ml), and for HVA was 69 ng/ml (normal for age  $125 \pm 8$ ) (ng/ml); when receiving treatment, 5-HIAA rose to 50 ng/ml, and HVA to 91 ng/ml.

In the infantile form of MTHFR deficiency, not only early diagnosis but excellent compliance with treatment are of paramount importance. Every cessation of treatment is followed by an irreversible deterioration in the child's condition. This treatment is complex and not easily accepted. We think that we might have obtained better results in this patient if she had not been kept with her family, but sent to a special children's home, to which the parents were strongly opposed.

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#### REFERENCE

1. Harpey J-P, Rosenblatt DS, Cooper BA, et al: Homocystinuria caused by 5,10-methylenetetrahydrofolate reductase deficiency: A case in an infant responding to methionine, folinic acid, pyridoxine, and vitamin B12 therapy. *J PEDIATR* 98:275, 1981.

### Possible teratogenic effect of valproate during pregnancy

#### To the Editor:

We report a prospective series of 14 infants born to epileptic women receiving valproate monotherapy during pregnancy. The daily doses of valproate ranged from 300 to 2000 mg. All the women had primary generalized epilepsy. Five women had grand mal seizures during pregnancy. Three infants (including twins) were prematurely born. One infant with multiple malformations was small for date and microcephalic. All other infants had birth measurements within the normal range (weight  $3363 \pm 527$  gm; length  $51.8 \pm 2.7$  cm; head circumference  $35.4 \pm 1.4$  cm). Five of the infants had a pattern of minor anomalies of the face and digits that had been partially described before.<sup>1,2</sup> The most prominent features were brachycephaly with high forehead, shallow orbits, small nose, microstomy, thin lips, low-set and rotated ears,