Long-term effects of antiepileptic therapy on cardiovascular risk factors in children

Sir,

Risk factors for atherosclerosis appear even in children, and early atherosclerotic changes begin to appear in childhood. One of the many new risk factors that is attracting ever greater scientific interest, and whose role in the development of atherosclerotic changes is indisputable, is homocysteine. Carbamazepine (CBZ) and valproic acid (VPA) lower serum folate and vitamin-B12 levels and increase homocysteine levels. The purpose of our study was to evaluate total plasma homocysteine concentrations and other cardiovascular risk factors in children on long-term (over five years) antiepileptic therapy, and to attempt to identify possible relationship between homocysteine and the degree of vitamin deficiencies.

The study subjects included 60 children (32 female, 28 male, mean age: 8.5 ± 3 years, age range: 2,5-15 years) using CBZ and VPA and 30 age-, sex- and body mass index-matched healthy children as control subjects. Fasting samples were collected for plasma total homocysteine, serum vitamin B, serum folate, lipoprotein (a), ApoB and urine methylmalonic acid. Duration of CBZ and VPA therapy was 6.83 ± 1 .10 and 6.44 ± 1.07 years, respectively. Plasma total homocysteine (13.1 ± 5.4 vs. 8.6 ± 3 .5 μmol/l, $P <$ 0.001), urine methylmalonic acid (42.1 ± 51 vs. 8.3 ± 4 .6 mmol/mol creatinine, $P <$ 0.001), lipoprotein (a) (25.4 ± 29 .1 vs. 9.0 ± 3 .8 mg/dl, $P <$ 0.001) were significantly higher in children receiving CBZ and VPA when compared to control subjects. The study group had significantly lower serum vitamin B_{12}>(356 ± 115.8 vs. 513 ± 165.6 pg/ml, $P <$ 0.001), serum folate (6.8 ± 2.7 vs. 12.59 ± 4.6 ng/mL $P <$ 0.001), and ApoB (89.9 ± 15.9 vs. 68.6 ± 13.9 mg/dl, $P <$ 0.001) than control group. Plasma total homocysteine, serum folate and lipoprotein (a) levels were slightly higher in CBZ-receiving group when compared to VPA-receiving group, but with no statistical significance. However, urine methylmalonic acid levels were significantly higher in the CBZ group than in the VPA group (62.1 ± 65 .4 vs. 22.2 ± 13 .8 mmol/mol creatinine, P: 0.002).

In the present study, we demonstrated that homocysteine levels in children using CBZ and VPA were slightly higher than healthy subjects and also homocysteine levels was significantly associated with urine methylmalonic acid. The measurement of serum or urine concentrations of methylmalonic acid and plasma homocysteine metabolites related to vitamin B_{12} deficiency has been used to establish vitamin B_{12} deficiency at the biochemical level. In conclusion, we suggest that urine methylmalonic acid may be a reliable indicator for vitamin deficiencies in children under prolonged antiepileptic therapy.

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