PLATELET FUNCTION AND VALPROATE

The role of arachidonate metabolites in valproate-induced platelet dysfunction and hemorrhagic diathesis was investigated by ex vivo methods at the Albert Szent-Gyorgyi Medical University, Szeged, Hungary. Platelets isolated from patients receiving long-term valproate (VPA) therapy or carbamazepine (CBZ) as a control were labeled with C14 arachidonic acid. C14-eicosanoids were separated by thin layer chromotography and determined quatitatively by liquid scintillation. VPA, even in low concentrations, reduced the activity of the arachidonate cascade in platelets, inhibiting the synthesis of the platelet aggregator thromboxane A2. (Kis B, Szupera Z, Mezei Z et al. Valproate treatment and platelet function: the role of arachidonate metabolites. Epilepsia March 1999;40:307-310). (Reprints: Dr B Kis, Department of Pathophysiology, Albert Szent-Gyorgyi Medical University, Szeged, H-6701, Semmelweis u 1, PO Box 531, Hungary).

COMMENT. VPA may cause alterations in hemostasis and increase surgical bleeding. Thrombocytopenia and platelet dysfunction are suggested causes for the bleeding, and ex vivo experiments have demonstrated a VPA-induced inhibition of arachidonate cascade in the platelets, leading to reduced synthesis of platelet aggregators.

Phenytoin-associated thrombocytopenia is reported in a 2-year-old girl on the 11th day of therapy, with recovery 5 days after withdrawal of treatment. There were no signs of bleeding.

ANTIEPILEPTIC SKIN REACTIONS AND BRAIN TUMORS

The frequency of both severe and mild skin reactions in 289 adult patients with brain tumors treated consecutively (1988-93) with cranial radiation and AEDs was studied retrospectively by review of records at the Brigham and Women's Hospital, Boston, MA. Erythema multiforme had occurred in only one patient, whereas milder rashes occurred in 18% of exposures to AEDs, including 22% of exposures to phenytoin, compared with the expected rate of 5-10%. Most rashes (59%) occurred before the initiation of radiotherapy. An increased frequency of mild drug rashes among patients with brain tumors, especially primary tumors, is not related to radiation. The increased prevalence of erythema multiforme and Stevens-Johnson syndrome frequently reported in patients with brain tumors treated with phenytoin or carbamazepine and cranial irradiation was not confirmed. (Mamon HJ, Wen PY, Burns AC, Loeffler JS. Allergic skin reactions to anticonvulsant medications in patients receiving cranial radiation therapy. Epilepsia March 1999;40:341-344). (Reprints: Dr HJ Mamon, Department of Radiation Therapy, Joint Center for Radiation Therapy, 330 Brookline Ave, Boston, MA 02215).

COMMENT. The rare occurrence of severe skin reactions in brain tumor patients receiving AEDs and cranial radiation in this study might be explained by discontinuation of AED before starting radiation therapy or at the earliest sign of a mild rash. Previous reports of erythema multiforme in patients receiving cranial irradiation and phenytoin or carbamazepine have alerted neurosurgeons to this increased risk of severe skin reactions and prompted heightened vigilance for this hazardous complication. The increased incidence of mild AED skin reactions noted in this series of primary brain tumor patients is unexplained. Tapering of a dexamethasone treatment was not a dominant factor but may have contributed to development of skin rash. Stevens-Johnson syndrome can be life-threatening, and the prophylactic use of phenytoin or carbamazepine following

brain tumor surgery should be avoided when possible, especially if cranial irradiation is planned.

In a randomized prospective study of carbamazepine or phenytoin in 276 post-craniotomy patients, 37% suffered at least 1 seizure during a 6-24 month trial period, and the incidence of status epilepticus in the first week following surgery was higher in AED-treated patients than in untreated controls (8% cf 2%). The occurrence of seizures in the first post-operative week did not increase the likelihood of late epilepsy. Acute allergic skin rashes occurred in 13% of patients treated with CBZ or PHT. (Foy PM et al. 1992. see Progress in Pediatric Neurology II, 1994;pp137-8; and Vol III, 1997;pp143-4).

VASCULAR DISORDERS

COGNITIVE DEFICITS AND MRI IN SICKLE CELL DISEASE

The risk of subtle brain abnormalities in children with sickle cell disease (SCD) and their relationship to blood hematocrit was determined by prospective comparison of 50 patients and 52 controls studied at St Jude Children's Research Hospital, Memphis, TN. Using quantitative magnetic resonance imaging to measure T1 (spin-lattice relaxation time) in basal ganglia, and the Wechsler test of intelligence, patients by age 4 years showed a significantly lower T1 (evidence of structural changes at the cellular level) in basal ganglia and cortex, but not in white matter, and mild mental deficiency (IQ, 50-70) in 33%, compared to a published prevalence of 1.45% in controls. Routine conventional MRIs were read as normal. Both the subtle T1 abnormalities on MRI and cognitive deficits were associated with a low hematocrit (Hct). Patients with an Hct of less than 27% had significantly lower IQ scores and significantly lower gray matter T1, than those with an Hct >27%. SCD was associated with a 23-fold increase in risk of mild mental deficiency. (Steen RG, Xiong X. Mulhern RK, Langston JW, Wang WC. Subtle brain abnormalities in children with sickle cell disease: relationship to blood hematocrit. Ann Neurol March 1999;45:279-286). (Respond: R Grant Steen PhD, Department of Diagnostic Imaging, St Jude Children's Research Hospital, 332 N Lauderdale, Memphis, TN 38105).

COMMENT. Young children with sickle cell disease and low hematocrits are at risk of subtle brain abnormalities, only detected by quantitative MRI, and complicated by mild mental deficiency. Brain hypoxia is proposed as the mechanism of this subtle brain damage demonstrated in patients with SCD who are spared more obvious brain pathology, including stroke.

Psychometric tests of intelligence can be more sensitive to subtle neurological abnormalities than conventional MRI scanning in SCD. In the absence of quantitative MRI, the Wechsler IQ test should be used routinely to follow children with SCD, not affected by stroke. The authors suggest that aggressive prophylactic therapy should be considered for possible prevention of brain damage and cognitive impairments in young children with SCD.

In an Editorial in the same issue, Dr GJ Dover of Johns Hopkins University School of Medicine discusses the progressive nature of the neuropathology of SCD (Ann Neurol March 1999;45:277-8). Steen and associates, in the present article, demonstrate the earliest detectable evidence of diffuse tissue hypoxia in the gray matter, as measured by quantitative MRI and IQ tests. Heretofore, the progression of brain pathology in SCD was documented in three ways: 1) subclinical large-vessel occlusion shown by Doppler; 2) clinical and subclinical infarcts seen on CT/MRI radiographic imaging; and 3) increased incidence of massive intracranial