weeks to target dosages of 400 mg/d TPM, 2250 mg/d VPA, or placebo and then maintained for an additional 12 weeks. Neuropsychological test battery was administered at baseline and at end of titration and maintenance periods. Cognitive deficits associated with TPM relative to VPA were greater at the end of titration than at the end of maintenance. The majority of patients tolerated TPM without cognitive side effects. The statistical differences were due mainly to a small subset of patients who were more negatively affected by TPM. (Meador KJ, Loring DW, Hulihan JF et al. Differential cognitive and behavioral effects of topiramate and valproate. Neurology May 13, 2003;60:1483-1488). (Reprints: Dr KJ Meador, Department of Neurology, Georgetown University Hospital, 1st Floor Bles, 3800 Reservoir Road, NW, Washington, DC 20007).

COMMENT. In early trials of TPM, psychomotor slowing, memory impairment, attention deficits, confusion, and speech problems were reported in 20% of adults with partial seizures (Reife R et al. Epilepsia 2000;41 (suppl 1):S66-71). The TPM-associated cognitive deficits appeared to be related to a rapid escalation of the dosage. Deficits in cognition may be diminished by a more gradual introduction of TPM and by testing after more prolonged usage. Monotherapy is less likely to induce cognitive problems than add-on therapy (Gilliam FG, Veloso F. Epilepsia 1998;39 (suppl 6):56).

INFECTIOUS DISORDERS

EARLY DIAGNOSIS OF HERPES SIMPLEX ENCEPHALITIS

Records of 38 patients, 23 boys and 15 girls (ages 3 months to 16 years [42% ages 3-12 months]), seen between 1990 and 1997 with proven herpes simplex encephalitis (HSE), were reviewed retrospectively to determine the diagnostic reliability of polymerase chain reaction (PCR) results, in a study at the Neuropediatric Service, Hopital Saint Vincent de Paul, Paris, France. Neonatal and adult cases were excluded. The delay between the onset of symptoms and the initiation of treatment and the dose and duration of antiviral treatment were recorded. Patients were divided in 2 groups, according to their PCR results. Nasopharyngeal infections were recorded 1-10 days before the onset of encephalitis in 18 cases (47%). Clinical symptoms of HSE varied with age: Of 24 patients aged <3 years, 19 (79%) had partial febrile seizures, and 1 had a generalized febrile seizure; in 14 patients aged >5 years, febrile seizures occurred at onset in only 5 (36%). Seizures were associated with an altered state of consciousness in approximately 60%, and the others had meningeal irritation, altered behavior, or speech disorders. IV acyclovir was administered for 10-30 days, in a dosage of 30-70 mg/kg/day. The mean delay between the start of acyclovir and the first reported neurological symptoms was 1.5 days.

EEGs recorded in 29 children (76%) were obtained between days 0 and 1 in 80% of cases. EEG abnormalities present in 100% consisted of diffuse slow waves in 9 (31%) and focal slow waves in 20 (69%), of whom 11 were focal temporal and 7 had periodic discharges. Necrotic hemorrhagic brain lesions on CT scan or MRI, observed in 26 (84%) of 31 patients examined, were temporal in location in 12, parietal in 6, and temporoparietal in 4.

HSV PCR performed on CSF (mean, 2.2 samples per patient) obtained between day 0 and 3 in 33 patients was positive in at least 1 CSF sample in 28 (85%). HSV was

detected in the first CSF specimen from only 25 (76%) of 33 patients. Initial negative PCR results observed in 8 patients drawn before day 3 were significantly associated with a low level of protein and <10 leucocytes/mm^3 in CSF. PCR performed after day 3 in 9 of 33 patients was positive in 5 samples drawn on days 4-21 and negative in 4 drawn on days 8-25. The CSF protein was elevated (>0.50 g/L) in 13 (40%) of 33 patients, reaching 0.71 g/L in 20 PCR-positive samples; it was significantly lower (P=.0007) when PCR was negative. WBC in the CSF was elevated (>5 cells/mm^3) in 28 (88%) patients, with a mean count of 229/mm^3 in 24 PCR-positive samples; it was significantly lower (P=.0011) when PCR was negative. A diagnosis of primary HSE based on seroconversion was established in 6 of 32 patients tested. HSE secondary to reactivation or reinfection was diagnosed in 16 cases with HSV-specific IgG found at onset of symptoms.

A negative PCR in a child with clinical, EEG, and/or radiological findings suggestive of encephalitis should not delay administration of acyclovir and should not lead to interruption of therapy. Antiviral therapy should be administered as long as the diagnosis has not been excluded. (De Tiege X, Heron B, Lebon P, Ponsot G, Rozenberg F. Limits of early diagnosis of herpes simplex encephalitis in children: a retrospective study of 38 cases. Clin Infect Dis 15 May 2003;36:1335-1339). (Reprints: Dr Flore Rozenberg, Laboratoire de Virologie, Hopital Saint Vincent de Paul, 82 Ave Denfert-Rochereau, 75674 Paris Cedex 14, France).

COMMENT. Herpes simplex virus encephalitis (HSE) results from primary or recurrent infection and in infants beyond the neonatal period and children, HSE is manifested by fever, alterations in consciousness, and seizures (AAP Red Book 2000, 25th ed). Unusual CNS manifestations of HSV include Bell's palsy, trigeminal neuralgia, myelitis, and postinfectious encephalomyelitis. The prognosis of HSE is significantly improved by IV acyclovir treatment, provided that therapy is begun early. Since its development in 1991, PCR for HSV DNA performed on CSF is widely accepted for the early diagnosis of HSE (Schlesinger Y et al. J Pediatr 1995;126:234-241). Antiviral acyclovir is recommended immediately after CSF sampling when a diagnosis of HSE is suspected. A negative HSV PCR in 25% of cases when testing CSF at 0-3 days after onset of symptoms has lead to misdiagnosis of HSE. In these cases of suspected HSE, a repeat lumbar puncture is advised after a few days, without interruption of acyclovir therapy. Histological examination and viral culture of brain biopsy tissue may be necessary to confirm the diagnosis in PCR-negative cases. The AAP recommends treatment for 21 days with IV acyclovir.

The absence of fever and normal CT lead to difficulty in diagnosis in 4 of 6 children with proven HSE, presenting with focal seizures and altered consciousness (Cameron PD et al. Dev Med Child Neurol 1992;34:134-140). All cases had abnormal EEG findings. The EEG is a sensitive test that may be superior to CT and ultrasound in the early diagnosis of neonatal HSE (Mikati MA et al. Neurology 1990;40:1433-1437); the multifocal periodic EEG pattern with CSF pleocytosis is highly suggestive of the diagnosis. Early diagnosis is also facilitated by MRI with T2 weighted images showing multiple small disseminated lesions ((Schroth G et al. Neurology 1987;37:179). A rare presentation of HSE in children is a relapsing biphasic illness manifested by fever and seizures and accompanied by generalized or hemi-chorea (Pike MG et al. Arch Dis Child

1991;66:1242-1244). Autism is another unusual sequel to HSE (Gillberg IC. Dev Med Child Neurol 1991;33:920-924).

NEUROLOGIC COMPLICATIONS OF SMALLPOX VACCINATION

Smallpox and smallpox vaccination is reviewed from the Departments of Neurology, Yale University School of Medicine, New Haven, CT, and University of New Mexico School of Medicine, Albuquerque. Neurological complications of smallpox vaccination are a postvaccinial encephalopathy (PVE) in children under 2 years of age and postvaccinial encephalomyelitis (PVEM) in recipients over 2 years. Past experience showed that the mortality of PVEM was 10 to 50%. The neuropathology of PVEM suggests an immune-mediated illness. Many unanswered questions need to be addressed regarding the risks of PVEM and PVE after smallpox vaccination with newer vaccines, neuroimaging findings, the prevention of these complications, and optimal therapy. (Booss J, Davis LE. Smallpox and smallpox vaccination. Neurological implications. Neurology April (2 of 2) 2003;60:1241-1245). (Reprints: Dr John Booss, Neurology Service (200), VA Connecticut Health Care System, 950 Campbell Ave, West Haven, CT 06516).

COMMENT. The risks of the smallpox vaccine are reviewed in an editorial (Johnson RT. Neurology April (2 of 2) 2003;60:1228-1229). Rates of PVEM vary from 1 in 4000 to 1 in 80,000 after primary vaccination, and from 1 in 50,000 to 1 in 450,000 after revaccination. Long-term disabilities of survivors may reach 30%. A vaccination campaign involving a previously unvaccinated population less than 35 years of age would carry the highest risk of neurologic complications. In addition, approximately 10% of the US population has some immunodeficiency, resulting in a greater risk of cutaneous dissemination.

The outcome of acute disseminated encephalomyelitis (ADEM) in a long-term follow-up study of 84 pediatric patients is covered in Ped Neur Briefs Nov 2002;16:81-82. Childhood ADEM affects boys more frequently than girls, and recovery occurs in 90%. Residual disability in 10% is not related to MRI lesions at onset but it is correlated with the occurrence of optic neuritis. MRI shows bilateral, asymmetrical involvement of white matter of frontal and parietal lobes, lesions in deep grey matter including the thalamus, and corpus callosum and periventricular demyelination. The location of pathology based on MRI findings was similar to that described in ADEM following smallpox vaccination (Greenfield JG. Neuropathology London, Edward Arnold Publishers, 1958;201-205). Turnbull and McIntosh (1926) published the first description of the encephalomyelitis following vaccination against smallpox in 7 cases in London. These authors emphasized involvement of the ventral half of the pons. In Holland about the same time, 139 cases of post-vaccinial encephalomyelitis with 41 deaths were reported (Bouman and Bok (1927). Case-reports of similar lesions to post-vaccinial ADEM soon appeared following varicella (1927), measles (1926), influenza (1930), and smallpox (1927). An increase in strength of the vaccine and primary vaccination of many older children and adolescents were considered responsible for the epidemic of post-vaccinial cases in Great Britain and Holland in the years 1923-6. Glanzmann (1927) was the first to suggest that post-vaccinial ADEM was due to an antigen-antibody reaction.