COMMENT. The authors comment on the rare occurrence of brainstem HSV-2 encephalitis in a neonate, and the importance of diffusion-weighted MRI in diagnosis. HSV-2 is the most common cause of neonatal herpes infection, usually affecting premature infants, and transmitted from the mother during birth. The disease in the neonate is disseminated, localized to the CNS, or affects the skin, eyes, and mouth. CNS disease usually presents by the 2^{nd} or 3^{rd} week of life, and typically affects the cerebral cortex diffusely. (AAP Red Book 2^{rm} ed. 2006).

DEMYELINATING DISEASE

CLINICAL MANIFESTATIONS AND VIRAL TRIGGERS OF CHILDHOOD MULTIPLE SCLEROSIS: MULTINATIONAL STUDY

The clinical manifestations, outcome, and viral triggers in 137 children (<18 years old) with multiple sclerosis (MS) and 96 controls, enrolled between 2003 and 2006 from diverse multinational geographic regions, were studied by researchers from the Divisions of Neurology and Microbiology, The Hospital for Sick Children, Toronto; Stony Brook University Medical Center, USA; and other centers in Canada, USA, Argentina, Russia, Italy, and Sweden. Children enrolled from South America were younger than those from other regions (p<0.0001). Female-to-male ratio was 1.54:1 in the total, and 1.1:1 in children with a first attack at <10 years. The mean age at first attack was 11.0 years (range, 1.6-17.9). The first MS attack resembled acute disseminated encephalomyelitis (ADEM) in 22 (16%), mostly children less than 10 years old (mean age 7.4 [SD 4.2] years), and significantly younger than those with poly- or mono-focal presentations (mean ages, 11 - 12 years; p < 0.0001 - < 0.0005). Optic neuritis occurred in 30 (22%), 23 as a monofocal, single location event. Monofocal brainstem or cerebellar symptoms occurred in 25 (18%), and transverse myelitis in 31 (23%), usually as a polyfocal presentation and a component of ADEM. Monofocal features at first attack were more common in European patients, whereas polyfocal or multiple site involvement (including ADEM) was reported more often in South American children (p=0.0095). Permanent physical disability within 5 years occurred in 13%, and 17% had impaired academic performance, that was correlated with disease duration (p=0.02). Standardized assays for IgG antibodies found 86% of MS patients were seropositive for remote Epstein-Barr virus (EBV), compared with 64% of controls (p=0.025), irrespective of geographic location. EBV seroprevalence increased as a function of increasing age, and was associated with a 2.8 times greater likelihood of MS compared to controls, MS patients did not differ from controls in exposure to cytomegalovirus, parvovirus B19, varicella zoster virus, and herpes simplex virus. Children seropositive for both EBV and HSV were 3.2 times more likely to have MS, as compared to EBV-positive, HSV-negative children (p=0.02). Compared to controls, MS children showed no differences in the frequency of family history of MS, month of birth, sibling number, sibling rank, or exposure to young siblings. (Banwell B, Krupp L, Kennedy J, et al. Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. Lancet Neurol September 2007;6:773-781). (Respond: Dr Brenda Banwell, The Hospital for Sick Children, University of Toronto, M5G 1X8 Toronto, ON, Canada).

COMMENT. The prevalence of multiple sclerosis (MS) has increased over the past half century. A study in Norway found the incidence by year of onset increased 2-fold from 2.87/100,000 in 1950-54 to 5.57/100,000 in 1985-91.(Midgard R et al. **Brain** 1996;119:203-211). The increase was a general trend and was not explained by a change in age distribution. Interest in childhood onset MS has increased and several reports have appeared in the literature in the past decade, the most recent from Taiwan of 21 cases. (Weng W-C et al. **Pediatr Neurol** 2006;35:327-334)(**AAP Grand Rounds** 2007;17:30-31). A female-to-male ratio of 2.5:1 in Taiwanese children is greater than that in the above multinational study (1.54:1) and closer to that of a Canadian collaborative study of 3.2:1. (Orton S-M et al. **Lancet Neurol** 2006;5:932-936). The female preponderance for MS has increased in the past 50 years, and daughters of female MS patients have a 50-fold increase in risk of contracting MS. (Sadovnick AD et al. **Neurology** 1988;38:90-991). Heritable risk factors for MS, recently identified by a genomewide study, include alleles of interleuken-2-receptor gene

MS is usually considered an autoimmune disease, but the mechanism is unproven. Recent work supports a viral etiology, with Ebstein-Barr virus having an important role in the initiation and progression of symptomatic autoimmunity. (Lunemann JD et al. **Curr Neurol Neurosci Rep** 2007;7:253-258)(Lipton HL et al. **Ann Neurol** 2007;61:514-523). Human herpesvirus-6, not included in the multinational study, may play a lesser role triggering attacks in relapsing-remitting MS. (Alvarez-Laftente R et al. **Mult Scler** 2007;13:578-583). Noninfectious factors sometimes implicated in the etiology of MS include geographic, environmental determinants, and the change in risk among migrants. Cigarette smoking may contribute to the increases reported in the female/male ratio and MS incidence. Sunlight exposure and vitamin D may have a protective effect.(Ascherio A et al. **Ann Neurol** 2007;61:504-513). Clinical evidence in support of viral infection in etiology include the viral prodrome, usually upper respiratory in type, that occurs in approximately one half of childhood onset MS cases, and oligoclonal bands in the CSF.

DISSEMINATED ENCEPHALOMYELITIS AND MULTIPLE SCLEROSIS DIFFERENTIATION

The distinguishing features of acute disseminated encephalomyelitis (DEM) and multiple sclerosis (MS) are reviewed by researchers at Harvard Medical School, Boston, MA, and University of Zagreb, Croatia. Acute and recurrent DEM affect children more than adults. Symptoms of DEM such as fever, altered consciousness, aphasia, and meningism are rare in MS. CSF oligoclonal bands are also rare. Genetic factors are often involved in MS but they are absent in ADEM. MRI is the best method of distinguishing the two distinct diseases. In DEM or ADEM, the lesions are larger than the plaques found in MS, they enhance with gadolinium, and often involve the thalamus and basal ganglia. MRI McDonald criteria for the diagnosis of MS require one enhancing or nine T-2 lesions: one infratentorial and one juxtacortical; and three or more periventricular lesions. The demyelinating lesions are disseminated in both diseases but differ in form and size; in MS the plaques are small and have characteristic sharply defined borders, whereas in ADEM they are large and ill-defined, inflammatory and perivenous.

Both brain and spinal cord MRI should be obtained in cases of clinically isolated syndrome (CIS) suggesting demyelination. Spinal cord lesions in DEM are elongated,