Age-Dependent Mendelian Predisposition to Herpes Simplex Virus Type 1 Encephalitis in Childhood

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Objective To test the hypothesis that predisposition to childhood herpes simplex virus (HSV) type 1 encephalitis (HSE) may be determined in part by human genetic factors.

Study design A genetic epidemiologic survey of childhood HSE (onset at age 3 months to 15 years) over a 20-year period (1985-2004) was conducted throughout France (comprising 29 university hospital neuropediatric centers). A total of 85 children fulfilled the diagnostic criteria for inclusion. Family and personal histories were obtained by face-to-face interview for 51 patients.

Results No familial cases of HSE were identified in our survey; however, a high proportion (20%) of the children interviewed had a relevant family history: parental consanguinity (12% of patients), early-onset herpetic keratitis in a first-degree relative (6%), or both (2%). The narrow window of high susceptibility to HSE before age 3 years (62% of patients) further indicates that predisposition to HSE is tightly age-dependent.

Conclusions This survey suggests that childhood HSE, although sporadic, may result from Mendelian predisposition (from autosomal recessive susceptibility in particular), at least in some children. There likely is incomplete penetrance, however, which may reflect, at least in part, the impact of age at the time of HSV-1 infection. *(J Pediatr 2010;157:623-9)*.

Herpes simplex virus type 1 (HSV-1) encephalitis (HSE) is the most common cause of sporadic viral encephalitis in Western countries, occurring at a rate of 1-2 per 500 000 individuals per year.[1-4] Although HSE can affect patients at almost any age, there are 2 peaks of incidence, the first at age 6 months to 3 years, corresponding mainly to primary infection, and the second at age >50 years, probably reflecting viral reactivation.[4-6] The introduction of acyclovir treatment has considerably reduced HSE mortality, although neurologic sequelae are common, especially in young children.[1,7-9] Previous studies evaluating the clinical outcome of children with HSE treated with acyclovir have shown that although the overall mortality rate was low (2 deceased patients out of a total of 80), a substantial proportion (35%-62%) had significant neurologic sequelae.[10-12] Since the landmark identification of its viral etiology in 1941,[13] the pathogenesis of HSE has remained elusive. The reason why only a minority of children infected with HSV-1 develop this devastating central nervous system (CNS) disease also is unclear. Specific HSV-1 variants are unlikely to be involved in CNS invasion; there have been

CSF	Cerebrospinal fluid
CNS	Central nervous system
CT	Computed tomography
HSE	Herpes simplex virus type 1 encephalitis
HSV-1	Herpes simplex virus type 1
IFN	Interferon
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction

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no epidemics, and no known correlation with a particularly neurovirulent viral strain has been identified.[14,15] In addition, nonviral environmental factors are not likely to be involved, given that no preferential geographic or seasonal pattern of occurrence has been observed.[4,6] Children with HSE are otherwise healthy and normally resistant to other infections, particularly those caused by other viruses. Children with any of the multitude of conventional primary immunodeficiencies or with human immunodeficiency virus infection are not prone to HSE.[16,17]

We recently investigated 2 children with a unique association of mycobacterial disease and HSE. One carried mutations in *STAT1*, leading to abolished cellular responses to interferon (IFN)-γ and IFN-α/β,[18] and the other had mutations in *NEMO*, resulting in impaired production of IFN-γ and IFN-α/β.[19] The HSE in these patients was not isolated, but these are the first 2 reported cases of HSE owing to a Mendelian disorder resulting in impaired IFN-α–mediated immunity. Moreover, the fact that familial HSE occurred in 4 kindreds with an interval of several years between cases of HSE,[20-23] making recurrence due to a virulent strain of HSV-1 highly unlikely, strongly suggests a role for host genetic factors in the pathogenesis of isolated HSE. These data suggest that isolated HSE also might reflect a Mendelian predisposition, in which CNS immunity to HSV-1 is specifically impaired. Indeed, we recently provided proof of principle that childhood HSE may result from Mendelian predisposition through identification of the first 2 genetic etiologies of isolated HSE, autosomal recessive UNC-93B deficiency[24] and autosomal dominant TLR3 deficiency.[25] We further tested this hypothesis by carrying out a comprehensive genetic epidemiologic survey, analyzing the clinical and familial features of a large series of children with HSE identified in a French retrospective survey spanning a 20-year period from 1985 to 2004.

Methods

We began by identifying children diagnosed with HSE in France between 1985 and 2004. Pediatricians from 29 university hospital neuropediatric centers in France were asked whether they had treated a child with HSE between 1985 and 2004. If a positive response was obtained, then a physician from our group visited the pediatric unit to analyze the patient's medical records in detail. For inclusion in the study, a patient had to be age >3 months but <15 years at diagnosis and alive at the time of the survey. HSE diagnosis was based on compatible clinical, radiologic, and electrophysiologic signs of encephalopathy, along with at least one of the following biological criteria: (1) detection of HSV-1 nucleic acid by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) collected within the first 10 days of the disease; (2) detection of HSV antigen in CSF samples in early study years; and (3) a 4-fold increase in anti-HSV–specific IgG antibody levels detected by enzyme-linked immunosorbent assay in 2 CSF samples and/or 2 blood samples, one obtained during the first week of symptoms and the other obtained more than 3 weeks after the onset of disease.

We contacted the families of the enrolled patients to schedule a face-to-face interview. At these interviews, we collected additional information, including history of herpes infections and other infections in the patient and first-degree relatives (parents and siblings). A complete family tree was built for each patient, paying particular attention to consanguinity loops and geographic origin. The clinical outcome was evaluated carefully for 2 specific characteristics: (1) the existence of relapses, defined as the onset of new symptoms occurring after an initial improvement in the patient's clinical status and at least one month after completion of treatment,[26] and requiring a new course of treatment with acyclovir and, in some cases, corticosteroid therapy; and (2) the long-term outcomes of epilepsy and mental retardation. Mental retardation was assessed by classifying the patients into 4 cognitive groups: (1) patients with normal school achievement; (2) patients with significant academic difficulties but able to follow regular school programs; (3) patients in special education systems; and (4) patients in specific institutions requiring constant help. A blood sample was taken from each participating subject for further investigation. Informed consent was obtained from patients who had reached adulthood by the time of the survey or from the parents of minors. Guidelines for human experimentation stipulated by the Institutional Review Board of Necker Hospital were followed.

Biological Methods

Standard methods were used for the detection of HSV-1 in CSF samples by PCR.[27,28] In some of the older patients, HSV antigens were detected using an immunoassay described previously.[29] Anti-HSV antibody titers in blood and CSF were determined using a standard neutralization test or immunoenzymatic procedures. In some cases, the intrathecal synthesis of anti-HSV antibodies was evaluated by comparing the serum with the CSF ratio of anti-HSV antibody titers, as described elsewhere.[27] IFN-α levels in the CSF were determined with a previously described method adapted for clinical specimens.[30,31] A laboratory reference of human IFN-α standardized against the National Institutes of Health's Ga 023-902-530 reference was included in each titration. A value $\geq$4 IU/mL indicates a clear increase in IFN-α level and is generally considered to provide strong evidence of HSE in a suggestive clinical context.

Statistical Methods

Differences in frequencies according to categorical variables were assessed by the Pearson χ^2 test or Fisher exact test. Quantitative variables were compared using the 2-tailed Wilcoxon rank-sum test. All analyses were performed with SAS version 8 (SAS Institute, Cary, North Carolina). For calculating the expected distribution of the 85 cases of HSE under the hypothesis that this distribution follows the acquisition of primary infection, we considered the 5 age classes shown in Figure 1 (available at www.jpeds.com), designated 1-5 (1-3, 4-6, 7-9, 10-12, and 13-15 years, respectively). The expected number of cases with HSE in age class i was