CURRENT LITERATURE

EVIDENCE THAT INTRACTABLE TEMPORAL LOBE EPILEPSY IS INFLUENCED BY GENETIC AND ENVIRONMENTALLY ACQUIRED FACTORS

Detection of Human Herpesvirus-6 in Mesial Temporal Lobe Epilepsy Surgical Brain Resections

Donati D, Akhyani N, Fogdell-Hahn A, Cermelli C, Cassiani-Ingoni R, Vortmeyer A, Heiss JD, Cogen P, Gaillard WD, Sato S, Theodore WH, Jacobson S

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BACKGROUND: Human herpesvirus-6 (HHV-6), a ubiquitous β-herpesvirus, is the causative agent of roseola infantum and has been associated with a number of neurologic disorders including seizures, encephalitis/meningitis, and multiple sclerosis. Although the role of HHV-6 in human CNS disease remains to be fully defined, a number of studies have suggested that the CNS can be a site for persistent HHV-6 infection.

OBJECTIVE: To characterize the extent and distribution of HHV-6 in human glial cells from surgical brain resections of patients with mesial temporal lobe epilepsy (MTLE).

METHOD: Brain samples from eight patients with MTLE and seven patients with neocortical epilepsy (NE) undergoing surgical resection were quantitatively analyzed for the presence of HHV-6 DNA by using a virus-specific real-time polymerase chain reaction (PCR) assay. HHV-6 expression also was characterized by Western blot analysis and in situ immunohistochemistry (IHC). In addition, HHV-6–reactive cells were analyzed for expression of glial fibrillary acidic protein (GFAP) by double immunofluorescence.

RESULTS: DNA obtained from four of eight patients with MTLE had significantly elevated levels of HHV-6, as quantified by real-time PCR. HHV-6 was not amplified in any of the seven patients with NE undergoing surgery. The highest levels of HHV-6 were demonstrated in hippocampal sections ($\leq$23,079 copies/10^6 cells) and subtyped as HHV-6B. Expression of HHV-6 was confirmed by Western blot analysis and IHC. HHV-6 was co-localized to GFAP-positive cells that morphologically appeared to be astrocytes.

CONCLUSIONS: HHV-6B is present in brain specimens from a subset of patients with MTLE and localized to astrocytes in the absence of inflammation. The amplification of HHV-6 from hippocampal and temporal lobe astrocytes of MTLE warrants further investigation into the possible role of HHV-6 in the development of MTLE.

Surgical Outcome in Mesial Temporal Sclerosis Correlates with Prion Protein Gene Variant

Walz R, Castro RM, Velasco TR, Alexandre V Jr, Lopes MH, Leite JP, Santos AC, Assirati JA Jr, Wichert-Ana L, Terra-Bustamante VC, Bianchin MM, Maciag PC, Ribeiro KB, Guarnieri R, Araujo D, Cabalero O, Moura R, Salim AC, Kindlmann K, Landemberger MC, Marques W Jr, Fernandes RM, Serafini LN, Machado HR, Carlotti CG Jr, Brentani RR, Sakamoto AC, Martins VR

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BACKGROUND: Mesial temporal lobe epilepsy related to hippocampal sclerosis (MTLE-HS) is the most common surgically remediable epileptic syndrome. Ablation of the cellular prion protein (PrP^c) gene (*PRNP*) enhances neuronal excitability of the hippocampus in vitro and sensitivity to seizure in vivo, indicating that PrP^c might be related to epilepsy.

OBJECTIVE: To evaluate the genetic contribution of *PRNP* to MTLE-HS.

METHODS: The *PRNP* coding sequence of DNA from peripheral blood cells of 100 consecutive patients with surgically treated MTLE-HS was compared with that from a group of healthy controls adjusted for sex, age, and ethnicity ($n = 180$). The presence of *PRNP* variant alleles was correlated with clinical and presurgical parameters as well as surgical outcome.

RESULTS: A variant allele at position 171 (Asn$\rightarrow$Ser), absent in controls, was found in heterozygosis (Asn171Ser) in 23% of patients ($P < 0.0001$). The *PRNP* genotypes were not correlated with any clinical or presurgical data investigated. However, patients carrying the Asn171Ser variant had a five times higher chance of continuing to have seizures after temporal lobectomy [95% confidence interval (CI), 1.65 to 17.33, $P = 0.005$) than did those carrying the normal allele. At 18 months after surgery, 91.8% of patients with the normal allele at

codon 171 were seizure free, in comparison with 68.2% of those carrying Asn171Ser ($P = 0.005$).
CONCLUSIONS: The *PRNP* variant allele Asn171Ser is highly prevalent in patients with medically untreatable MTLE-HS and influences their surgical outcome. The results suggest that the *PRNP* variant allele at codon 171 (Asn171Ser) is associated with epileptogenesis in MTLE-HS.

COMMENTARY

Two recent reports of intractable temporal lobe epilepsy patients who underwent surgical resection suggest that effects of a common environmental viral exposure may be a causative factor and that a subtle genetic variation may influence its intractability. In the first report, Donati et al. studied brain surgical specimens for the presence of human herpesvirus-6 (HHV-6). HHV-6 is a ubiquitous β-herpesvirus, often acquired in early childhood, which causes the usually benign and self-limited infection known as roseola infantum (exanthum subitum). The virus also has been shown to infect astrocytes, among other cell types. In eight patients with mesial temporal lobe epilepsy (MTLE), both hippocampus and lateral temporal lobe specimens were evaluated. HHV-6 was detected in four of eight hippocampal surgical specimens, and in two of these four, the virus was detected in the lateral temporal lobe as well. In all four of the HHV-6–affected patients, the number of viral copies per 10^6 cells was higher in the hippocampal specimens than in the lateral temporal lobe specimens, suggesting that the virus is trophic for the hippocampus. In light of the likely exposure to HHV-6 in early childhood, the age at onset of epilepsy was evaluated and not found to be different between the patients with and without HHV-6 in brain specimens.

The authors also evaluated seven subjects with neocortical epilepsy (NE), four of whom had frontal resections, and HHV-6 was not detected in any surgical specimen. Only two hippocampal and four lateral temporal specimens were obtained in this group, so comparison of the trophism of the virus between these two types of epilepsies is difficult. Overall their findings do suggest, however, that exposure to HHV-6 may influence the development of intractable MTLE as compared with NE.

Can exposure to HHV-6 be evaluated routinely in epilepsy patients by testing peripheral blood samples or by historical information? The evidence suggests that, as yet, these procedures are not reliable. Donati et al. studied 13 of their 15 epilepsy patients and 23 controls for the presence of HHV-6 in peripheral blood mononuclear cells, and all were negative—even though four of the MTLE patients' brain specimens were positive. Peripheral blood, therefore, does not provide reliable information that would indicate the presence of HHV-6 in the brain. In a similar study, Uesugi et al. (1) found 6 of 17 TLE patients to have positive surgical specimens for HHV-6. Two of the group of 17 had exanthum subitum exposure in infancy with status epilepticus; however, neither had positive brain specimens for HHV-6 at surgery. Thus a history of exposure to exanthum subitum also does not reliably correlate to the presence of HHV-6 in the brain.

Walz et al. studied 100 patients with MTLE who underwent temporal lobectomy for the presence of a cellular prion protein gene (*PRNP*) variant and found that 68.2% of those with the allelic variation were seizure free compared with 91.8% of those without the variant. The exact variant is Asn/Ser heterozygosity instead of Asn/Asn homozygosity at codon 171. Twenty-three of the 100 subjects carried the variant, compared with none of the 180 healthy control subjects. The patients' outcome was assessed 18 months after surgery, and all antiseizure medications remained unchanged over this period.

Walz et al. pointed out that the *PRNP* is a reasonable target to evaluate for effects on clinical epilepsy because ablation of this gene causes increase neuronal excitability in experimental systems. They also found an allelic variation at codon 129 that tended to be overrepresented in the epilepsy group compared with controls. Although the results did not quite reach statistical significance, the authors indicate that a relation to epileptogenesis may be suggested by this finding. The presence of the *PRNP* variant allele is obviously only a partial indicator of a less favorable surgical outcome; however, the findings by Walz et al. indicate that its presence may be a risk factor for seizure recurrence after epilepsy surgery. Although the *PRNP* variant allele currently is not a clearly established risk factor for intractability, in the future it may prove to be so, along with other genetic factors under exploration. It is detected by genotyping from whole blood samples; therefore it is a simple procedure for patients.

These two studies are exciting in that they lead the field of epilepsy beyond seizure phenomena, seizure localization, and historical features as influences on epilepsy intractability and toward other, more objective markers of epileptogenesis. Both the presence of HHV-6 in the brain and the inheritance of the *PRNP* variant allele may be contributing factors to the intractability of epilepsy, specifically MTLE, in the case of HHV-6. Allelic variations of *PRNP* also may be important to the development of epilepsy. Neither of these findings can be readily applied in the clinic as yet, but methods to detect these factors could be developed, should they continue to prove of clinical importance.

by Cynthia L. Harden, M.D.

Reference

1. Uesugi H, Shimizu H, Maehara T, Arai N, Nakayama H. Presence of human herpes virus 6 and herpes simplex virus detected by polymerase chain reaction in surgical tissue form temporal lobe epileptic patients. Psychiatry Clin Neurosci 2000;54:589–593.