Hippocampal sclerosis: An inflammatory hypothesis

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An inflammatory hypothesis

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Temporal lobe epilepsy is the most commonly encountered partial epilepsy syndrome in adults. Many patients are refractory to medications and therefore considered for surgical treatment. Pathologic series and modern imaging demonstrate evidence of hippocampal (mesial temporal) sclerosis (HS), characterized by cell loss in the hippocampal pyramidal cell layer and hilus with associated volume loss and gliosis, in a substantial fraction of affected individuals. Human and animal studies indicate that HS may be the consequence or the cause of chronic epilepsy, or in some cases, both. While many patients with HS have seizures beginning in childhood, the discovery of hippocampal pathology in patients with adult onset seizures is not uncommon and the etiology often remains obscure. In this issue, Bien and colleagues offer provocative evidence suggesting that up to half of such patients may develop epilepsy as a consequence of limbic encephalitis.[1]

Limbic encephalitis (LE) is a syndrome that subsumes both paraneoplastic and non-neoplastic inflammatory conditions resulting in behavioral and cognitive abnormalities, with or without seizures, with associated limbic system abnormalities on MR imaging. Paraneoplastic LE requires either demonstration of antineuronal antibodies or emergence of a malignant neoplasm within 5 years of onset of neurologic dysfunction.[2] Especially when the latter criterion is applied, the definition may lack adequate specificity to define a homogeneous cohort of patients. For example, an individual with AD and progressive hippocampal atrophy and gliosis who develops carcinoma could be misclassified as having LE. Importantly, the full spectrum of antineuronal antibodies that may result in LE remains incompletely defined.

While attack on CNS tissue by antineuronal autoantibodies is generally thought to be the cause of LE, a causative role for identified antibodies has not been established.[3] Passive transfer experiments have not been successful in recreating the disease in animal models. Moreover, no general mechanism whereby an antibody-mediated process produces dysfunction of an anatomically discrete system has been demonstrated.

In the study by Bien and colleagues, 9/38 patients fulfilled the authors' criteria for definite LE, including 5 meeting the PNS Euronetwork criteria,[4] of whom 2 had antineuronal antibodies. Four additional patients were classified as having definite LE based on the presence of anti-voltage-gated potassium channel (VGKC) antibodies. Although the precise pathophysiology of seizures with anti-VGKC antibodies is unclear, these patients indicate that epilepsy must be added to the list of phenotypic presentations of inflammatory channelopathies, along with ataxia in paraneoplastic cerebellar degeneration and neuromuscular junction failure in Lambert Eaton myasthenic syndrome, both associated with anti-voltage-gated calcium channel autoantibodies.

Bien et al. used MRI criteria to define 11 additional cases which they termed possible limbic encephalitis, relying on evidence of early hippocampal swelling, continuous increased T2 signal, and progressive atrophy; one of these cases had atypical anti-Hu antibodies. No evidence is provided, however, to establish the specificity of these imaging findings, and experienced epileptologists have observed this pattern of progression in patients examined after febrile convulsions, status epilepticus, and recurrent temporal lobe seizures of diverse etiologies.[5,6] Nonetheless, the finding that patients with definite or possible LE were more likely than those with other etiologies to have bilateral HS is particularly intriguing in the context of a putative autoimmune mechanism. Interestingly, this is at odds with the unilateral presentation that is the clinical hallmark of another inflammatory epilepsy, Rasmussen chronic encephalitis.

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Histopathologic examination revealed evidence of an inflammatory process in one of two patients classified as possible LE who underwent epilepsy surgery. Pathologic analysis was not available in the remaining 18 cases considered to represent definite or possible LE. Classic bland HS is described in the remaining 7 patients who underwent epilepsy surgery. The relative lack of pathologic data in this report is troublesome and leaves the reader unable to fully assess the claim that LE is the cause of many cases of adult-onset epilepsy with HS. If the assertion is true, then the paucity of inflammatory pathology in other large surgical epilepsy series indicates that epilepsy must outlive the active phase of its putative inflammatory etiology. A natural corollary would then seem to be that use of immunomodulatory treatment once epilepsy is established will be of little utility.

Important limitations of Bien and colleagues' study are its retrospective nature and incomplete data ascertainment. For example, antibodies known to be associated with limbic encephalitis were assayed in only 3/18 patients judged to have non-immune mediated HS, and 16/20 patients considered to have definite or possible LE-associated HS. Some of those patients had anti-onco-neuronal—but not anti-VGKC—antibodies assayed. No control group was identified, thus the prevalence of autoantibodies in patients with seizure disorders is unknown. Because these authors have a longstanding interest in limbic encephalitis, the possibility of referral bias cannot be eliminated. Finally, the authors did not study children or adolescents; thus we have no information on whether an analogous process may lead to epilepsy in younger patients.

Several important points require further study. It is possible that seizures trigger an autoimmune process in susceptible individuals. Imaging studies demonstrate transient breakdown of the blood–brain barrier after single or repeated seizures,[6] offering an opportunity for attack on CNS antigens. Moreover, because seizures cause neuronal injury, it is possible that novel antigenic epitopes may be exposed as the result of recurrent or prolonged events. Under these scenarios, the discovery of antineuronal antibodies in patients with epilepsy may be an epiphenomenon of little pathophysiologic importance. On the other hand, there is growing evidence that immunomodulatory molecules may directly affect neuronal excitability.[7] Perhaps it is through the liberation of neuroactive cytokines and inflammatory modulators that both infectious and noninfectious autoimmune encephalidities cause seizures, especially when such illnesses are anatomically directed against epileptogenic structures such as the limbic system. The first set of issues, which revolve around the question of causation, will require careful prospective study in large clinical populations. The second, concerning pathophysiology of epilepsy in patients with active inflammatory diseases, are most likely to be resolved in experimental systems where the chemical and immunologic milieu can be controlled. For now, it is likely that the report of Bien et al. will trigger more aggressive searches for immunomarkers in patients with focal epilepsy of unknown cause, whatever their age.

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