Limbic Encephalitis: Another Example of Molecular Mimicry?

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Limbic encephalitis (LE) is more frequent than once thought [1]. Its etiologies can be divided between viral and autoimmune disorders. In the latter group, several autoantibodies, which can or cannot be of paraneoplastic origin, have been associated with LE. Among the most recently described autoantibodies, one finds those directed against voltage-gated potassium channels [2] or those that recognize the neuropil [3]. However, many novel cell membrane antibodies await further characterization [3, 4]. Viral causes of LE are mostly due to herpetic viruses, such as herpes simplex virus 1 in immunocompetent or human herpes virus 6 in immunocompromised patients. A role for nonherpetic viruses, however, is not well established [5].

The paper of Nakajima et al. [6] in this issue of *European Neurology* is interesting as it suggests that viral and autoimmune causes of LE might be reconciled. These authors report the case of an immunocompetent, tumor-free patient who presented with recurrent episodes of LE. He recovered from the first two episodes, but the third one left him severely impaired with major cognitive dysfunction and sleep apnea syndrome. In the CSF contemporary to the first two episodes, enterovirus RNA was detected by PCR. However, in subsequent lumbar punctures, enterovirus was no longer present, but immunoglobulins G (IgG) specific for the glutamate receptor $\epsilon 2$ were repeatedly detected. The subsequent presence, in the CSF, of a virus and then of a CNS autoantibody is puzzling and it is tempting to hypothesize that this is not a coincidental association.

Microbial infections have been associated with autoimmune diseases for a long time and for varied diseases such as multiple sclerosis, diabetes or myocarditis. Molecular mimicry is a mechanism frequently called upon to explain this relationship. This mechanism postulates that some autoantigens have epitopes in common with microbes [7]. One of the best examples of molecular mimicry is rheumatic fever. In this disorder, monoclonal antibodies that recognize group A β -hemolytic streptococci also react against heart, joints, brain and skin [8]. Guillain-Barré syndrome is perhaps the most convincing example of molecular mimicry in the neurological field. In some individuals, *Campylobacter jejuni* infection can induce antibodies that cross-react with lipo-oligosaccharide in the bacterial wall and gangliosides, leading to polyradiculoneuropathy [9]. However, in addition to antibodies, some virus-specific T cells are probably able to cross-react with autoantigen. For example, although this is still controversial, molecular mimicry is thought to be a major component in the immunopathogenesis of multiple sclerosis. Lang et al. [10] demonstrated that a T cell clone from a multiple sclerosis patient was able to recognize autoantigen (myelin basic protein) as well as viral (Epstein-Barr virus) epitopes, whereas these two peptides shared no obvious sequence similarities and were presented each by a different HLA class II protein. This fascinating experiment shows that molecular mimicry can go well beyond the simple structural resemblance of two individual peptides.

In the patient of Nakashima et al. [6], whether enterovirus-specific antibodies could have cross-reacted with epitope(s) present on the glutamate receptor $\varepsilon 2$, and be instrumental in the immunopathogenesis of the LE, remains purely hypothetical. Clearly, additional observations of LE with such an association of virus and autoantigen are warranted. In addition, laboratory experiments to study putative cross-reactivity of immunoglobulins between enterovirus and glutamate receptor $\varepsilon 2$ epitopes should be undertaken. This might represent a daunting

task as the group of enterovirus actually encompasses many different viruses. Finally, such studies should not be restricted to antibodies but also examine a hypothetical T cell cross-reactivity. Nevertheless, if additional observations suggesting a link between viruses and autoimmunity in LE are made, such studies might be worth the workload. Indeed, the need for a better understanding of LE pathogenesis, from a clinical as well as from a biological standpoint, is clearly established [11].

References

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