Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis.

Abstract:
Classical paraneoplastic encephalitis syndromes with 'onconeural' antibodies directed to intracellular antigens, and the recently described paraneoplastic or non-paraneoplastic encephalitides and antibodies against both neural surface antigens (voltage-gated potassium channel-complexes, N-methyl-d-aspartate receptors) and intracellular antigens (glutamic acid decarboxylase-65), constitute an increasingly recognized group of immune-mediated brain diseases. Evidence for specific immune mechanisms, however, is scarce. Here, we report qualitative and quantitative immunopathology in brain tissue (biopsy or autopsy material) of 17 cases with encephalitis and antibodies to either intracellular (Hu, Ma2, glutamic acid decarboxylase) or surface antigenic targets (voltage-gated potassium channel-complex or N-methyl-d-aspartate receptors). We hypothesized that the encephalitides with antibodies against intracellular antigens (intracellular antigen-onconeural and intracellular antigen-glutamic acid decarboxylase groups) would show neurodegeneration mediated by T cell cytotoxicity and the encephalitides with antibodies against surface antigens would be antibody-mediated and would show less T cell involvement. We found a higher CD8/CD3 ratio and
more frequent appositions of granzyme-B(+) cytotoxic T cells to neurons, with associated neuronal loss, in the intracellular antigen-onconeural group (anti-Hu and anti-Ma2 cases) compared to the patients with surface antigens (anti-N-methyl-d-aspartate receptors and anti-voltage-gated potassium channel complex cases). One of the glutamic acid decarboxylase antibody encephalitis cases (intracellular antigen-glutamic acid decarboxylase group) showed multiple appositions of GrB-positive T cells to neurons. Generally, however, the glutamic acid decarboxylase antibody cases showed less intense inflammation and also had relatively low CD8/CD3 ratios compared with the intracellular antigen-onconeural cases. Conversely, we found complement C9neo deposition on neurons associated with acute neuronal cell death in the surface antigen group only, specifically in the voltage-gated potassium channel-complex antibody patients. N-methyl-d-aspartate receptors-antibody cases showed no evidence of antibody and complement-mediated tissue injury and were distinguished from all other encephalitides by the absence of clear neuronal pathology and a low density of inflammatory cells. Although tissue samples varied in location and in the stage of disease, our findings strongly support a central role for T cell-mediated neuronal cytotoxicity in encephalitides with antibodies against intracellular antigens. In voltage-gated potassium channel-complex encephalitis, a subset of the surface antigen antibody encephalitides, an antibody- and complement-mediated immune response appears to be responsible for neuronal loss and cerebral atrophy; the apparent absence of these mechanisms in N-methyl-d-aspartate receptors antibody encephalitis is intriguing and requires further study.