

## Anti-NMDA receptor encephalitis: Pathogenic mechanisms and treatment algorithm

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Since the discovery of anti-NMDA receptor encephalitis in 2007, it has become the most frequent and best studied CNS disorder caused by antibodies to cell surface or synaptic proteins. The disorder preferentially affects young women, although men and children can also be affected. The association with an underlying tumor, usually a teratoma, varies according to the patient's age, gender, and ethnicity. The associated neuropsychiatric syndrome develops in stages and is highly predictable, with limited variation among individuals and age. The antibodies are directed against the N-terminal domain of the NR1 subunit of the NMDAR, and their levels, relative to total IgG, are always higher in CSF than serum. Multiple studies have confirmed an intrathecal synthesis of antibodies probably by the meningeal- and brain-infiltrating plasma cells. *In vitro* and *in vivo* studies show structural and functional effects of the antibodies resulting in a specific reduction of the levels of synaptic NMDAR by a mechanism of antibody capping, cross-linking and internalization of the re-

ceptors. These effects correlate with the antibody titers and are reversible upon removing the antibodies. In addition, the antibodies abrogate NMDAR-mediated currents potentially altering the mechanisms of synaptic plasticity. Cortical injection of antibodies results in an increase of glutamate release, enhancing the excitability of the motor cortex. Autopsy studies have confirmed a decrease of NMDAR levels in the brain regions with higher concentration of antibodies. Overall, these antibody effects coupled with the characteristic clinical syndrome resemble those predicted from models of genetic or pharmacological decrease of NMDAR function. All of these findings must be considered for the development of treatment strategies that should be directed not only to remove antibodies from serum but also to abrogate the inflammatory infiltrates and synthesis of antibodies within the CNS.

※The authors declare there is no conflict of interest relevant to this article.