

# NMDA receptor autoimmunity in mania following HSV encephalitis

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Herpes simplex virus (HSV) encephalitis (HSVE) is the commonest cause of death in cases of sporadic encephalitis in humans (Johnston, 1998) with relapse occurring in approximately 12% of patients (Skoldenberg *et al.* 2006). While commonly attributed to viral reactivation, it is increasingly recognised that a proportion of 'relapses' are due to anti-NMDA receptor encephalitis (NMDARE), a treatable autoimmune disorder caused by IgG autoantibodies against the NR1 subunit of the *N*-methyl-D-aspartate (NMDA) receptor (Armangue *et al.* 2015). While the proportion of clinical relapses from HSVE attributable to NMDARE remains unknown, a study found 25% of HSVE patients had anti-NMDA receptor antibodies in CSF after three months (Westman *et al.* 2016). Affective symptoms have been described as a presenting symptom of HSVE, as well as a sequel (McGrath *et al.* 1997), although the underlying mechanisms have not been elucidated. We report the case of a manic episode associated with transient NMDA receptor autoimmunity occurring as a sequel to HSVE.

A 37-year-old male with an unremarkable medical history was admitted to hospital with headaches and subsequently suffered a generalised seizure and cardio-respiratory arrest. MRI revealed acute restricted diffusion in the right mesial temporal lobe and a cerebrospinal fluid (CSF) sample was positive for HSV type 1 (HSV-1). He was treated with intravenous acyclovir and discharged with residual symptoms of headache, fatigue and bilateral tremor of the upper limbs.

One month later he was brought back to the hospital with a 4-day history of paranoia and insomnia. On arrival he was distractible and preoccupied with colours and numbers and highly agitated, requiring intramuscular sedation. Neurological examination revealed gaze impersistence and saccadic intrusion of smooth pursuit, fine tremor with superimposed myoclonic jerks and subtle perioral myoclonus. The neuropsychiatric assessment revealed manic symptoms including social disinhibition, elation, increased self-esteem and tangential thoughts.

Initial blood results revealed elevated C-reactive protein (23 mg/L) and neutrophil count ( $7.9 \times 10^9/L$ ). Serum anti-NMDA receptor antibody using a live cell-based assay was low positive (scoring 1.5 on a 0–4 scale at 1 : 20 dilution and 0.5 at 1 : 100 dilution). Serum anti-VGKC and onconeural antibody screen were negative. CSF revealed elevated protein (784 mg/dL) and white blood cells (9 cells/ $\mu$ ), as well as unmatched oligoclonal bands. A CSF and serum viral screen, which included HSV-1 PCR, was negative.

MRI head revealed a signal abnormality, with swelling within the right anteromesial temporal lobe and dorsal frontal lobe extending into gyrus rectus and posteriorly into the ipsilateral parietal and occipital lobes with the blurring of grey-white matter differentiation, in keeping with recent HSVE. EEG revealed a delta brush-like appearance, a pattern reported to be highly specific for NMDARE (Schmitt *et al.* 2012).

He was commenced on IV acyclovir prior to excluding a viral aetiology and thereafter treated with regular clonazepam 1mg BD, leading to a partial reduction of his manic symptoms and he was discharged after 2 weeks. Repeat serum anti-NMDA receptor antibody assay was negative and EEG was normal, while MRI showed resolving signal hyperintensity and reduced swelling, with some persisting signal abnormality in the right anteromesial temporal lobe. Repeat neuropsychiatric assessment revealed resolution of manic/psychotic symptoms and cognitive impairment (see Fig. 1).

The case expands the likely clinical manifestations of post-HSVE NMDA receptor autoimmunity, as well as suggesting a plausible explanation for some of the cognitive and affective changes occurring after HSVE.

Evidence supporting the pathogenic relevance of NMDA receptor autoimmunity includes the characteristic delta brush-like waves, unmatched oligoclonal bands and temporal association between the antibody and affective status. Possible mechanisms by which HSV infection could cause neuronal autoimmunity include (a) limbic damage leading to exposure of NMDA receptor epitopes triggering a second immune response and (b) molecular mimicry. An alternative



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