

CASE REPORT

Anti-NMDA-receptor antibody-mediated cortical blindness: a case report

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Learning point for clinicians

- In the presence of any unexplained neurological disorder, carefully review all available tissue pathology.
- Bank serum, cerebrospinal fluid and DNA in all patients with undiagnosed neurological disorders
- Always try to obtain consent for autopsy in patients with undiagnosed neurological disorders. Anti-N-methyl-D-aspartate receptor encephalitis was described just 8 years ago but it clearly accounts for many undiagnosed and misdiagnosed encephalitides. Our report will increase awareness of the range of clinical presentations of a treatable neurological disorder.

A 73-year-old woman underwent laparotomy for perforated duodenal ulcer, presumed secondary to non-steroidal use for back pain. An incidental ten centimetre ovarian dermoid cyst was also resected. Post-operatively she developed sepsis, acute kidney injury, type two respiratory failure, and a transient drop in Glasgow Coma Scale (GCS). Computed tomography (CT) brain was normal. Her level of consciousness recovered spontaneously and she was discharged home symptom-free.

Two days later, she re-presented with generalized seizures. CT brain did not show any acute changes. Cerebrospinal fluid (CSF) constituents were normal. She became encephalopathic, with refractory seizures. Examination revealed cortical blindness and right-sided neglect. Electroencephalography (EEG)

demonstrated right posterior hemispheric periodic lateralized epileptiform discharges (PLEDs). Repeat CT brain showed loss of grey-white matter differentiation within the left parietal lobe which was not present on CT two weeks earlier; magnetic resonance imaging (MRI) demonstrated high signal in the same area. Serum NMDA-receptor antibodies were positive and intravenous immunoglobulin (IVIG) was commenced. A generalized bullous rash developed and skin biopsy confirmed Stevens-Johnson syndrome, presumed secondary to phenytoin therapy. Repeat MRI brain showed interval progression (Figure 1A). Posterior thalamic hyperintensities raised the possibility of Creutzfeldt-Jakob disease. Death from septic shock occurred on Day 38.

At post mortem, gross coronal sections of the cerebral hemispheres revealed parieto-occipital petechial haemorrhages. (Figure 1B) Brain microscopy demonstrated profound changes in both occipital cortices, with pan-cortical gliosis and virtual total neuronal loss. Gliosis was confirmed with GFAP immunohistochemistry. Widespread rod-shaped microglial activation was confirmed with CD68 antibodies. There was no cortical lymphocytic infiltration. The thalamus showed moderate gliosis. Immunohistochemical staining for alpha-synuclein, tau, beta A4, TTP43 and P63 was negative. Proteinase K-resistant prion protein was not expressed. Histologic review of the ovarian dermoid cyst resected prior to autopsy revealed mature neural tissue.

Discussion

In this brief case report, we describe the development of rapidly progressive cortical blindness with seizures, occurring in

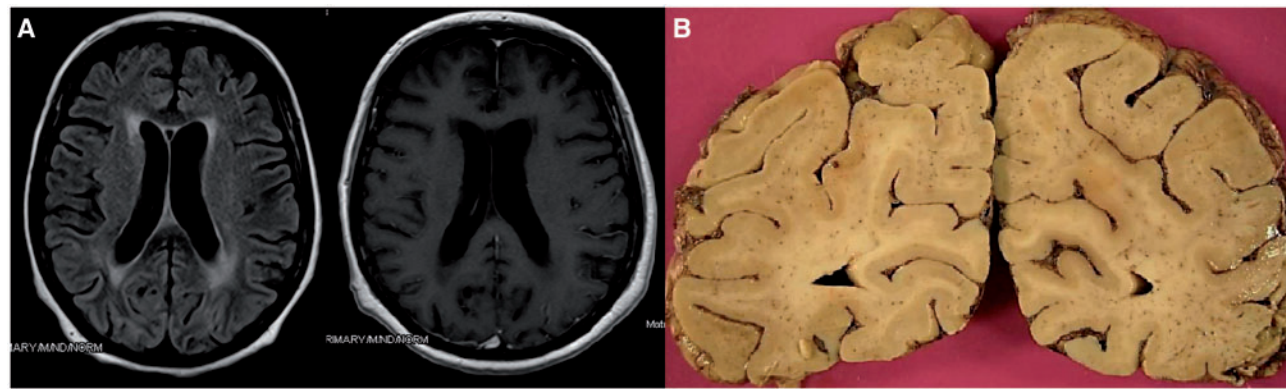


Figure 1. (A) Axial MRI brain studies show high signal in left occipital cortex on FLAIR image and subtle post-contrast leptomeningeal enhancement on T1-weighted post-gadolinium image. (B) Cross section of occipital region at post mortem examination of the brain.

association with a benign ovarian teratoma and which we believe to have been mediated by NMDA-receptor antibodies.

The mechanism of NMDA-mediated neuronal injury is one of immune cross-reactivity. Fab fragments of NMDA-receptor IgG antibodies bind to, cap and cross-link NMDA-receptors in the brain resulting in internalization of the receptors, decreasing the synaptic density of NMDA clusters. This decreases NMDA-mediated currents (predominantly GABAergic neurons) leading to a disinhibition of the excitatory pathways and increased extracellular glutamate.¹ Early immunotherapy improves outcome.² Older patients experience delays in treatment, conferring a worse prognosis.³

The neuropathology is noteworthy for the extent of gliosis and neuronal loss in both occipital cortices. A bilateral parieto-occipital disease process had been suggested by clinical examination, EEG abnormalities and radiological findings. Tazun described the neuropathologic findings in two patients with anti-NMDA-receptor encephalitis.⁴ Increased reactive microglia were common to his cases and ours. In all three, a lymphocytic infiltrate was uncommon. In a study of 400 patients, 98% of tumours associated with anti-NMDA-receptor encephalitis were ovarian teratomas.¹ Dabner described five teratomas with lymphocytic aggregates and a perineural tissue infiltration pattern similar to that described in our case.⁵

Differential diagnoses of this patient's symptoms include hypoxic-ischaemic encephalopathy (HIE) and posterior reversible encephalopathy syndrome (PRES). Indeed, laminar or pancortical necrosis of the isocortex and gliosis of the thalamus are characteristic of HIE. However, the sequence of clinical events is not supportive of HIE or of PRES. Although there was sepsis and a drop in GCS (which may have been an unrecognized post-ictal state); there were no hypotensive episodes, brain imaging was normal and neurological recovery was complete. Refractory seizures without systemic cause were the dominant neurological presentation with subsequent progression to encephalopathy and later development of structural imaging alterations with the emergence of PLEDs. MRI brain showed abnormalities which had progressed two weeks later. In HIE-related laminar cortical necrosis, it is usual to find neurons in varying stages of necrosis exhibiting classic 'red and dead' cytoplasmic eosinophilia associated with an ongoing response to HIE. None were present.

As in all paraneoplastic neurologic disorders, the clinical expression of NMDA-mediated encephalitis may occur at any time before, during or after the discovery of the underlying tumour without any overt precipitant. We believe that the teratoma was

present long before onset of neurologic symptoms. It is possible that the patient's back pain was due to an enlarging teratoma, which led to non-steroidal use and a resultant duodenal ulcer. The first CSF sample was not tested for NMDA-receptor antibodies. The second sample tested negative. However, this was after initiation of immunotherapy with IVIG. Furthermore, a recent paper has described how low serum levels of NMDA-receptor antibodies, often associated with negative CSF, are clinically significant in a proportion of cases.⁶

The drop in GCS might have been due to hypotension which led to cortical necrosis and cortical blindness but such a hypotensive episode was not recorded. Consequently, we are of the opinion that in the absence of any other pathologic process, NMDA-receptor antibodies on a background of occult ovarian teratoma, induced profound occipital neuronal injury resulting in cortical blindness. Pancortical gliosis in bilateral occipital cortices and neuronal loss to this extent has not previously been described in anti-NMDA-receptor encephalitis.

Conflict of interest: None declared.

References

- Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci* 2010; **30**:5866–75.
- Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008; **7**:1091–8.
- Titulaer MJ, McCracken L, Gabilondo I, Iizuka T, Kawachi I, Batailler L, et al. Late-onset anti-NMDA receptor encephalitis. *Neurology* 2013; **81**:1058–63.
- Tuzun E, Zhou L, Baehring JM, Bannykh S, Rosenfeld MR, Dalmau J. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. *Acta Neuropathol* 2009; **118**:737–43.
- Dabner M, McCluggage WG, Bundell C, Carr A, Leung Y, Sharma R, et al. Ovarian teratoma associated with anti-N-methyl D-aspartate receptor encephalitis: a report of 5 cases documenting prominent intratumoral lymphoid infiltrates. *Int J Gynecol Pathol* 2012; **31**:429–37.
- Zandi MS, Paterson RW, Ellul MA, Jacobson L, Al-Diwani A, Jones JL, et al. Clinical relevance of serum antibodies to extracellular N-methyl-D-aspartate receptor epitopes. *J Neurol Neurosurg Psychiatry* 2015; **86**:708–13.