Delayed NMDA Receptor Encephalitis Relapse in a Male Patient

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Here, we report a case of a 36 year old man with antibody-confirmed NMDA receptor encephalitis who was admitted at age 15 with a similar presentation, representing a delay to first relapse of 21 years. Our patient presented at age 36 with a 10-day history of progressive word finding difficulties and paranoid ideation, preceded by URTI symptoms. On admission examination, he was bradyphrenic with expressive aphasia, short term memory impairment, and executive dysfunction. He had left beating gaze-evoked nystagmus and orofacial dyskinesias, but no other cranial nerve, sensorimotor, or cerebellar abnormalities. Empiric ceftriaxone and acyclovir were started. A lumbar puncture showed elevated protein (1395 mg/L) and WBC (56 X10^6 cells/L- 82% neutrophils). Viral PCR was negative. Contrast MRI head was unremarkable. EEG showed changes suggestive of extreme delta brush pattern (Figure 1). He progressed to frank psychosis and florid agitation by post-admission day 2, and autonomic disturbance with altered temperature regulation and sinus tachycardia by day 7. IVIG (2g/kg) was started at day 5, followed by a 5 day course of IV methylprednisolone at day 10 given no early response to IVIG. IVIG was initiated before steroids due to concern about exacerbating psychosis. NMDA receptor antibodies returned strongly positive in the serum and CSF. Neoplastic screen (CT of the chest, abdomen, and pelvis, with testicular ultrasound) was negative. He continued to deteriorate to a nonverbal state by day 14. Due to lack of response to immunotherapy, plasma exchange (PLEX) was performed at day 20, and Rituximab (1g IV X 2 doses 2 weeks apart) started after PLEX at post-admission day 30. His neurological status improved markedly over 3 weeks following 5 cycles of PLEX. On discharge at day 50, he had marked improvement with a Montreal Cognitive Assessment (MoCA) score of 25/30. After
further active rehabilitation, at 1 year follow-up he returned to baseline and is working at his
previous level of function.

Medical records were reviewed for his presentation at age 15, with a 4-week history of acute
confusional state, starting as intermittent memory difficulty and progressed to bizarre
behaviour, mutism, and psychomotor retardation. Initial examination revealed hypophonia,
inappropriate smiling, and delusions of reference without cranial nerve, sensorimotor, or
cerebellar abnormalities. Initial investigations including brain CT scan and routine CSF studies
were normal, with negative infectious work up. His first EEG showed a dysrhythmic pattern
with left temporal sharp waves in sleep state. Autoimmune antibody testing for inflammatory
causes was not performed, as this was not available in 1998. Over the next few weeks, he
deteriorated into a non-verbal, catatonic state with hyperthermia. He was treated empirically for
neuroleptic malignant syndrome, possibly related to antipsychotics started for his behavioural
state. He had two clinical seizures with left hemispheric onset and was treated with phenytoin
and phenobarbital. Repeat EEG showed diffuse theta activity with left temporal sharp waves.
Extensive workup for vasculitis, rare infections, and inborn errors of metabolism was negative.
Contrast MRI brain was normal. Skin and right frontal brain biopsy did not show areas of
inflammation. Despite this, empiric immunosuppression with pulse IV methylprednisolone for
presumed inflammatory CNS disease was started. A week later, he exhibited signs of
improvement. His antiepileptic medications were weaned without further seizures. He
recovered over the next year, completed high school, a bachelor’s degree, and started his own
business. Table (1) contrasts his two presentations.

NMDA receptor encephalitis is an immune-mediated neurological syndrome presenting with
personality change, memory loss, and behavioural abnormalities, often progressing to
psychosis, seizures, movement disorders, autonomic dysfunction, hypoventilation, and coma
(1). An underlying neoplasm is detected in approximately 40-60% of patients, the majority of
which are ovarian teratomas; the remainder of cases are presumed to be autoimmune (1-3).
Autoimmune causes of encephalitis are common and early identification of a compatible
syndrome, exclusion of infectious causes, and application of appropriate immune therapy can
significantly improve survival and outcome in these patients. In a cohort study of 501 patients,
Titulaer et al (3) demonstrated 69 relapses in 45 patients at two years, defined as ‘the new onset
or worsening of symptoms occurring after at least two months of improvement or stabilization.’
23/69 relapses were comparable or more severe than previous episodes. Relapse rate was higher
in patients without a tumour. This suggests that a period of monitoring for relapse may be
required. The long period of quiescence in our case is unusual for NMDA receptor encephalitis.
Time to first relapse varies in the literature, with a median delay of 18-24 months (2,4); in one
patient, a longer delay of up to 13 years was reported (4). Relapse risk was higher in patients
without a tumour and those who did not receive immune-therapy at the onset of disease.
Dalmau et al. (2018) describe two main emerging pathophysiological mechanisms by which
antibodies to central nervous system proteins may arise (1). The first mechanism involves
leakage of CNS antigens across the blood-brain barrier during episodes of viral encephalitis.
The second mechanism is by expression of CNS antigens on tumor cells in the periphery. It has
been suggested that relapses may indicate recurrence of the initial tumour or presence of an
undiagnosed malignancy. In our patient, HSV was not isolated in CSF during either presentation nor was a tumour found. It has been shown that serum antibody titres do not correlate with disease relapse and are not useful for monitoring but that CSF antibody titres do correlate with disease activity (5). However, serial CSF analysis is not a practical method of monitoring for relapse over time owing to its invasiveness. At this time, monitoring for relapse remains clinical. Patients and family members should also be educated about the signs and symptoms of relapse that should prompt re-evaluation by a neurologist.

In conclusion, NMDA receptor encephalitis is a treatable condition if recognized early. Factors associated with long delays to relapse are unknown. Development of a registry of NMDAR patients for long term follow-up, now that the antibody is well characterized and commonly tested, may more precisely clarify the natural history and outcomes of this condition.

Statement of authorship

SA, MA, JL, and CU drafted the manuscript and revised the content. JM reviewed, critiqued, and edited the manuscript.

Declaration of conflicting interests

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References


Table 1. Comparison of childhood (presumed autoimmune encephalitis) and adult presentation (definite NMDA-R encephalitis) clinical and laboratory features

<table>
<thead>
<tr>
<th>Finding</th>
<th>Childhood Presentation (Age 15)</th>
<th>Adulthood Presentation (Age 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal Behaviour/Cognitive Dysfunction</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Speech Dysfunction/Mutism</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Seizures</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Movement Disorder/Abnormal Postures</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Decreased Level of Consciousness</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Autonomic Dysfunction</td>
<td>Information unavailable</td>
<td>✓</td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CSF abnormalities</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NMDA receptor Antibody</td>
<td>Not performed</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
Figure 1. EEG in bipolar montage demonstrating diffuse moderate amplitude frontally predominant 0.5 to 1 hz delta activity with superimposed high-amplitude frontally predominant discharges (right more than left) suggestive of “extreme delta brush”. The background consists of moderate amplitude, well-developed 8-9 hz alpha posterior dominant rhythm. (Sensitivity 7 mA, 60 hz filter on).