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Case Report

Long duration between presentation of probable anti-N-methyl-D-aspartate receptor encephalitis and either clinical relapse or positive serum autoantibodies

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune encephalitis first described in 2007. This condition has a well-characterised clinical phenotype with a multistage presentation beginning with prodromal symptoms, psychosis, cognitive deficits, and seizures, which can progress to involve movement disorders, catatonia, autonomic instability, and central hypoventilation requiring ventilatory support. Our first patient demonstrates, to our knowledge, the longest duration between the presentation of anti-NMDAR encephalitis and clinical relapse that has thus far been described. Our second patient highlights a clinical scenario where positive serum autoantibodies are demonstrated six years following complete clinical recovery, in the absence of clinical features of a relapse or a malignancy on screening. These patients highlight the importance of long-term follow up and tumour surveillance, and the role of electroconvulsive therapy in the management of catatonia. These cases also support the need for future studies evaluating the role of maintenance immunosuppression in patients at high risk for relapses.

1. Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune encephalitis first described in 2007.[1] It has a well-characterised clinical phenotype beginning with prodromal symptoms, psychosis, cognitive deficits, and seizures, which can progress to involve movement disorders, catatonia, dysautonomia, and hypoventilation.[1–3] Specific antibodies against the NR1/NR2B heteromers of the NMDAR have been identified as pathological.[4] The presence of an associated malignancy, most commonly an ovarian teratoma, has been demonstrated in 10–56% of patients.[4,5] The following cases highlight the potential for delayed relapse and the need for long-term follow up.

2. Case reports

2.1. Patient 1

A 31-year-old woman presented in 2011 with a one-week history of a viral prodrome and two generalised seizures. She demonstrated psychosis and an excited catatonia. She had a similar presentation fifteen years ago, resulting in a ten-month admission, but had made an excellent recovery.

A diagnosis of relapsing anti-NMDAR encephalitis was confirmed on antibody testing of serum and cerebrospinal fluid (CSF) on her second presentation. There was no detectable malignancy. As treatment with intravenous methylprednisone, immunoglobulin, and plasma exchange did not result in sustained improvement, second line therapy with rituximab was undertaken with good effect.

2.2. Patient 2

A 17-year-old girl presented with acute psychosis and severe catatonia in 2005. Her absence of response to regular benzodiazepines prompted a trial of electroconvulsive therapy (ECT). She improved significantly within two weeks and completely recovered over the span of one year.

The working diagnosis at presentation, prior to the first reports of anti-NMDAR encephalitis, was catatonia secondary to a viral or autoimmune encephalitis. Due to patient preference, testing for serum anti-NMDAR antibodies was delayed for six years, but finally confirmed in 2011. Detailed investigations did not reveal a malignancy.

Full details of the clinical presentation, investigations, and management for both cases are included as Supplementary Data. Although we did not have documented anti-NMDAR antibody positivity at the time of initial presentation in either patient, the

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clinical, CSF, and electroencephalographic features were typical in both patients, and other causes were reasonably excluded.

3. Discussion

Relapses occur in 15–25% of patients with anti-NMDAR encephalitis.[4] Patient 1 is unique as, to our knowledge, there have been no reports of such a long asymptomatic interval as fifteen years between a presumed index episode and relapse. Lack of immunotherapy at disease onset, delayed tumour removal, or failure to identify a tumour have been identified as risk factors for relapses, and these were present in both patients.[1,2,4,5]

Iizuka et al.[6] retrospectively analysed sera and CSF at initial presentation of four women with a prior diagnosis of "juvenile acute nonherpetic encephalitis" and demonstrated anti-NMDAR antibody positivity. Ovarian teratomas were demonstrated in three patients up to seven years from presentation. None had positive antibodies at follow-up. The implications of anti-NMDAR antibody positivity six years after clinical recovery, in the absence of a relapse or malignancy on screening in Patient 2, remain uncertain. There is some suggestion that the antibody titre parallels clinical improvement in patients.[7] This is the longest documented persistent antibody positivity after clinical remission thus far described, and raises the spectre of subclinical pathological autoantibody production due to an occult malignancy or inflammatory trigger.[6] It also heightens the index of suspicion for future relapses, and reinforces the need for ongoing tumour surveillance.

Both patients demonstrated complete recovery without immunomodulatory therapy or tumour identification. Spontaneous resolution has been reported with anti-NMDAR encephalitis, at the expense of prolonged hospitalisation and slower recovery.[1,6] To our knowledge, Patient 2 is only the second report of complete recovery with ECT as the sole therapeutic intervention, the first being described recently by Matsumoto et al.[8] There have been only a few reports of a response to ECT in patients with confirmed anti-NMDAR encephalitis,[1] although the role of ECT in paraneoplastic catatonia has been noted previously.[4,8–10] Possible explanations for its efficacy include the upregulation of NMDA receptors or modulation of glutamatergic synapses as shown in animal models.[8,9]

In patients without an identified tumour, periodic screening for ovarian teratomas and other malignancies are currently recommended for at least two years.[1] It should be noted that positron emission tomography scans may be noncontributory in patients with ovarian teratomas, so a variety of imaging modalities should be utilised to thoroughly evaluate the patient for associated neoplasms. We propose that in patients without identified tumours, and particularly in those in whom the initial episode was not treated with immunomodulatory therapy, the period of ongoing tumour surveillance and antibody titre monitoring should be extended by as much as ten years. ECT could be considered in patients with anti-NMDAR encephalitis and prominent catatonia, who are refractory to targeted immunomodulatory therapy. Future studies are required to evaluate the role of maintenance immunosuppression in patients at high risk for relapses.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jocn.2012.10.023.

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