Electroconvulsive therapy and/or plasmapheresis in autoimmune encephalitis?

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Abstract

Autoimmune encephalitis is a poorly understood condition that can present with a combination of neurological and psychiatric symptoms, either of which may predominate. There are many autoantibodies associated with a variety of clinical syndromes - anti-N-Methyl-D-Aspartate receptor (NMDAR) is the commonest. Currently, the most widely used therapy is prompt plasmapheresis and steroid treatment (and tumour resection if indicated), followed by second line immunosuppression if this fails. Given the growing awareness of autoimmune encephalitis as an entity, it is increasingly important that we consider it as a potential diagnosis in order to provide timely, effective treatment. We discuss several previously published case reports and one new case. These reports examined the effects of electroconvulsive therapy (ECT) on patients with autoimmune encephalitis, particularly those in whom psychiatric symptoms are especially debilitating and refractory to standard treatment. We also discuss factors predicting good outcome and possible mechanisms by which ECT may be effective. Numerous cases, such as those presented by Wingfield, Tsutsui, Florance, Sansing, Braakman and Matsumoto, demonstrate effective use of ECT in anti-NMDAR encephalitis patients with severe psychiatric symptoms such as catatonia, psychosis, narcolepsy and stupor who had failed to respond to standard treatments alone. We also present a new case of a 71-year-old female who presented to a psychiatric unit initially with depression, which escalated to catatonia, delusions, nihilism and auditory hallucinations. After anti-NMDAR antibodies were isolated, she was treated by the neurology team with plasmapheresis and steroids, with a partial response. She received multiple sessions of...
ECT and her psychiatric symptoms completely resolved and she returned to her premorbid state. For this reason, we suggest that ECT should be considered, particularly in those patients who are non-responders to standard therapies.

Key words: Autoimmune encephalitis; Electroconvulsive therapies; Autoantibodies; Plasmapheresis

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Core tip: Although there are still only a small number of reports supporting the theory that electroconvulsive therapies is effective in treating symptoms of autoimmune encephalitis, it is reasonable to suggest that it should be considered as an alternative/adjunct to standard immunosuppressive therapies. There is a difficulty in differentiating between "functional" causes of psychosis and psychosis seen in anti-N Methyl D Aspartate receptor encephalitis, which may lead to some patients being treated inappropriately with antipsychotics rather than immunomodulatory treatments. It is crucial for clinicians to be aware of the potential for patients to present to either psychiatry or neurology services to allow timely diagnosis and prompt, appropriate treatment.

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INTRODUCTION

It has been established that autoantibody mediated encephalitides can present with altered mental states[1-3]. Psychiatric presentation of autoimmune encephalitis has attracted considerable interest since the association with autoantibodies was discovered, particularly as many of these syndromes have demonstrated excellent responses to immunomodulatory therapies and may be underdiagnosed[11]. Anti N-Methyl-D-Aspartate receptor (NMDAR) encephalitis appears to be the commonest form, followed by anti-Voltage Gated Potassium Channel (VGKC) mediated encephalitis (which actually encompasses a number of subtypes including anti Leucine-rich Glia Inactivated 1 (LG11) and Contactin-Associated Protein 2 (CASPR2)). Other antibodies associated with encephalitis with psychiatric presentations are anti Gamma-Aminobutyric Acid A (GABA-A), Gamma-Aminobutyric Acid B (GABA-B), Glutamate Decarboxylase (GAD) and α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolpropionic Acid (AMPA) receptor antibodies[4]. Presentation appears to differ according to the associated antibody. Anti LG11 encephalitis presents with “a classic limbic encephalitis” but also rapid eye movement (REM) sleep disorders and occasionally movement abnormalities. Patients with anti-CASPR2 encephalitis tend to develop Morvan syndrome which is characterized by a limbic encephalitis, neuromyotonia and autonomic features[5,6]. Anti-GAD associated encephalitis presents as “stiff man syndrome”, with cerebellar ataxia and seizures, although psychiatric symptoms may also feature[5,7]. Those with anti-GABA-B encephalitis develop seizures early on in their presentation, alongside memory loss, confusion and hallucinations[5,8]. Anti-AMPA encephalitis is predominantly a paraneoplastic phenomenon, which presents with limbic encephalitis, confusion, memory impairment, seizures and psychosis[5,9].

The presentation in anti-NMDAR mediated encephalitis initially appeared to follow a predictable timeline, with a viral-type prodrome followed by neuropsychiatric symptoms, then subsequent movement abnormalities and autonomic dysfunction[9,10]. Short term memory loss, personality and behavioural changes, language disintegration (including reduced verbal output or mutism), psychosis, paranoia, agitation and catatonia have been the most commonly described psychiatric presentations in this type of autoimmune encephalitis[10-13]. However, further studies have shown that anti-NMDAR encephalitis may not follow this progressive stepwise presentation and can present with isolated psychiatric symptoms[5,11], or have relapses with isolated psychiatric symptoms[14] which then makes consideration of possible autoimmune aetiology in the psychiatric setting even more crucial.

Early treatment in autoimmune encephalitis accelerates recovery, reduces ongoing disability and prevents relapse[13]. It is important to initially exclude an underlying neoplastic process with computed tomography (CT), magnetic resonance (MR) or positron emission tomography (PET) imaging. In the absence of any malignancy, the recommended treatment is prompt and aggressive immunotherapy[1,3]. Plasmapheresis or intravenous immunoglobulins in combination with corticosteroids is the first line therapy. A review of over 500 patients with anti-NMDAR encephalitis showed that 53% of those treated with immunosuppression (and tumour removal if indicated) made improvement within 4 wk[15]. Further immunosuppressive drugs are often required if this first line therapy fails – cyclophosphamide and rituximab are the most commonly used[2].

Interestingly, other treatments including electroconvulsive therapy (ECT) have also been used and found to be at least partially effective in a number of cases[9,16-18]. Indeed, several patients have made extraordinary recoveries after ECT administration, with improvement in stupor, catatonia, psychosis and delusions[19].

Braakman presented a case of a 47-year-old previously healthy male who presented with progressive psychiatric symptoms following an upper respiratory tract infection[19]. Extensive investigations were performed,
including multiple CT and MR images, which did not reveal any abnormality. Cerebrospinal fluid (CSF) showed a pleocytosis and the patient received therapy initially for a viral encephalitis and subsequently for encephalitis lethargica (with intravenous lorazepam and 3 d of intravenous methylprednisolone). His psychiatric symptoms failed to resolve and he therefore underwent 7 sessions of bilateral ECT, which eventually induced remission. All symptoms, including mutism, hallucinations, oculogyric crises and extrapyramidal symptoms resolved and he returned to work within 2 years. Retrospective analysis of his CSF revealed anti-NMDAR antibodies and this was therefore concluded to be anti-NMDAR encephalitis. A further case reported by Matsumoto described an 18-year-old Japanese male who presented with delusions, catalepsy, convulsions and involuntary tongue movements following influenza. Initial investigations did not reveal a diagnosis and he was treated initially for catatonic schizophrenia with antipsychotics, lorazepam and valproate, which failed to provoke sufficient clinical response. He proceeded to receive 13 sessions of ECT and made a complete recovery. Again, CSF results only became available after discharge, which were also positive for anti-NMDAR antibodies.

**CASE REPORT**

A 71-year-old previously healthy female presented to her general practitioner (GP) in October 2013 with malaise and bilateral shoulder pain. Her erythrocyte sedimentation rate (ESR) was raised at 45 mm/h and C-reactive protein (CRP) levels were noted to be raised and she was therefore commenced on treatment for presumed Polymyalgia Rheumatica with Prednisolone at 15 mg once per day (OD) for 3 wk and continued on a reducing dose. She started to show signs of low mood at the start of her course of steroids, accompanied by obsessional thoughts about her boiler exploding and paranoid thoughts about her husband wanting to harm her. She presented to her GP following completion of her steroids and was prescribed Fluoxetine, Buspirone and Diazepam to alleviate these symptoms following advice from a psychiatrist.

The patient’s mental health continued to deteriorate despite these measures in the community. She lost 2 stones in weight and was unable to fulfill her activities of daily living (ADLs). She developed severe depressive symptoms with catatonia, posturing with psychotic symptoms, paranoid thoughts nihilistic delusions and auditory hallucinations, so was admitted informally to a psychiatric ward in November 2013.

At the time of admission she appeared withdrawn, confused, disorientated and was responding to auditory hallucinations. General physical examination was normal and there were no abnormal neurological findings. Her bloods on admission revealed a raised ESR, white cell count (with neutrophilia), raised urea and creatinine and raised alanine transaminase (ALT) and bilirubin. Lumbar puncture for CSF analysis was not felt to be indicated at this time. A CT scan of her head did not demonstrate any abnormality.

The patient received a trial of several psychotropic medications initially - Risperidone and Sertraline, which were titrated up to 5 mg and 100 mg respectively. Shortly afterwards, she became dizzy and had an unresponsive episode so was admitted to the emergency department for further investigations. No physical cause was identified and her Risperidone and Sertraline were stopped. She was subsequently treated with maximal doses of Mirtazapine, Venlafaxine and Olanzapine, which also failed to significantly improve her symptoms. She remained severely depressed with persistent catatonia and psychotic features so she was commenced on an ECT regime. She received 4 cycles of ECT until she unfortunately fell, sustaining a fractured neck of femur, which required an operation and a 2 wk admission to an orthopaedic ward.

On return to the psychiatric unit in January 2014, the results of the autoantibody screen sent on admission became available which showed that her serum sample was low positive for anti-NMDAR antibodies. She was therefore referred to the Neurology team for their input in management in light of the new diagnosis of anti-NMDAR encephalitis.

Magnetic Resonance Imaging (MRI) of her head at this time was normal. A CT scan of her chest, abdomen and pelvis did not identify an ovarian teratoma or any other evidence of malignancy. Electroencephalogram (EEG) performed indicated a post-central dominant Rhythm at 9 Hz up to 90 mV, which spread to the anterior regions. A considerable amount of theta activity was noted which was diffusely present, especially over the temporal regions and a slight slowing was occasionally noted over the temporal areas bilaterally.

The patient was transferred to a Neurology unit to receive plasmapheresis in March 2014 after careful consideration that this was a new onset severe psychiatric syndrome that was treatment resistant. She received 5 d of plasma exchange and was administered Methylprednisolone 1 g IV for 3 d, followed by Prednisolone at 1 mg/kg OD, which was then tapered down. Her anti-NMDAR antibody levels remained at a “low positive” level post-plasmapheresis. Her mood and speed of thinking were noted to improve and this was corroborated by an improvement in serial addenbrooke’s cognitive examination revised (ACE-R) tests, although she remained severely depressed and her paranoia worsened after 1-2 mo. She was transferred back to the psychiatric unit and received Quetiapine, Lithium and further Venlafaxine. She continued on reducing doses of Prednisolone.

Even despite the plasmapheresis, corticosteroids and multiple psychotropics, the patient’s symptoms remained severe. The psychiatric team therefore decided to embark on a second course of ECT. The patient received a further 8 cycles of ECT in May 2014 (approximately 2 mo after completion of plasmapheresis) and made a rapid and
marked recovery. Her mood improved significantly with no psychotic symptoms or perceptual abnormality. Her anti-NMDAR antibody titre was repeated and were undetectable. She began to function at her premorbid level and was discharged home in July 2014 with Lithium, Venlafaxine, Quetiapine and Prednisolone. The improvement in the patient’s symptoms after the second course of ECT was remarkable. It is difficult to know how much improvement was due to either her immunosuppressive therapies or the ECT - it is more likely that the combination of both led to her recovery. At 6 mo follow up, the patient presented well with no significant affective, psychotic or cognitive symptoms. She was compliant with her medication, had good insight into her illness and had made further progress since discharge, corresponding with an improvement in her scores in the addenbrooke’s cognitive examination, Geriatric Depression Scale and Brief Psychiatric Rating Scale (Tables 1 and 2).

**DISCUSSION**

Diagnosis of these encephalitides is supported by identification of antibodies in CSF or serum, however the decision to embark on immunotherapy is usually made depending on the patient’s clinical condition rather than the actual antibody titre. Of note, the identification of NMDAR antibodies does not automatically confirm a diagnosis of anti-NMDAR encephalitis- this result should always be considered with the clinical presentation in mind. Research by Zandi et al[21] showed that NMDAR-Abs were higher in patients with associated tumours. Low positive and positive results were found in a spectrum of patients including those classified as having a possible NMDAR encephalitis and in unlikely cases. Some of those with low positive results were later diagnosed with neurodegenerative disorders and responded poorly to immunotherapy.

There is very little research that has explored how best to monitor patients and whether serum or CSF titre is needed but they appear to correlate with clinical progress[5]. Predictors of good outcome are less severe clinical symptoms at onset, no admission to an intensive care unit and timely initiation of immunomodulatory therapy[15]. Interestingly, Titulaer et al[13] in 2013 suggested that the rate of recovery can be extremely variable - some patients in this study stopped attending follow up assessments due to an accelerated recovery phase, whereas others were still making more modest progress two years later.

The exact mechanism behind ECT in autoimmune encephalitis is unclear. ECT has previously been shown to upregulate NMDAR in animal models. Watkins et al[22] showed that ECT caused an elevation in mRNA for some NMDA subunits (NR2A and NR2B) in rats, mainly in the dentate gyrus of the hippocampus, although these changes only lasted for 48 h. A study done by Fumagalli et al[23] in 2010 suggested that ECT may aid regeneration of NMDAR damaged by autoantibodies by improving binding of the glutamate subunit on NMDA in the hippocampus[22]. Another idea is that use of ECT results in partial resolution of symptoms, leading to exposure of other features of the disease which can then be targeted and treated[13].

At present, the concept of autoimmune encephalitis is relatively new and poorly understood. It is important for clinicians working in both psychiatry and neurology to be aware of the potential for patients to present to either specialty. Education in this field is needed to raise awareness of these treatable, but potentially fatal conditions - for example one could easily mistakenly treat those presenting to a psychiatric setting with antipsychotics and those presenting to a medical

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**Table 1** Table demonstrating changes in the patient’s addenbrooke’s cognitive examination-III scores throughout admission and after discharge.

| ACE-III | During admission 13/01/2014 | Later during admission 24/02/2014 | 1 mo post plasma exchange 17/04/2014 | 6 mo post ECT and discharge date 30/01/2015 |
|---------|-----------------------------|----------------------------------|------------------------------------|---------------------------------|
| Total score | 82/100                      | 79/100                           | 68/100                             | 92/100                          |
| Attention | 15/18                        | 15/18                            | 10/18                              | 16/18                           |
| Memory   | 22/26                        | 23/26                            | 17/26                              | 26/26                           |
| Fluency  | 10/14                        | 3/14                             | 3/14                               | 9/14                            |
| Language | 23/26                        | 24/26                            | 23/26                              | 25/26                           |
| Visuospatial | 12/16                   | 14/16                            | 15/16                              | 16/16                           |

ECT: Electroconvulsive therapy; ACE-III: Addenbrooke’s Cognitive Examination-III.

**Table 2** Table illustrating the change in geriatric depression scale and brief psychiatric rating scale scores from admission to post-electroconvulsive therapy and discharge.

| Geriatric depression scale | Brief psychiatric rating scale |
|---------------------------|-------------------------------|
| 23/01/2014                | 30/01/2015                   |
| During admission          | 6 mo post electroconvulsive therapy and discharge date |
| 30/01/2015                | 15/05/2014                   |
| During admission          | 6 mo post ECT and discharge date |
| Score 20/30 (severe depression) | 0/30 (Normal)               |
| 84 (moderate to severe psychosis) | 18 (Normal)                |
setting may not receive ECT. "Red flags" for these diagnoses should be noted so that the appropriate investigations can be performed promptly, to allow early commencement of treatment and to secure the best outcomes. Furthermore, many of these patients will require joint neurology and psychiatry input, depending on which symptoms are present and which of these predominate.

In view of several case studies demonstrating the role in autoimmune encephalitis, ECT may be emerging as a viable alternative or adjunct to immunomodulatory therapies, particularly in those with prevailing psychiatric symptoms. Further studies are needed to establish its role either alone or in combination with other treatments.

**COMMENTS**

**Case characteristics**
A 71-year-old previously well female presented with low mood and psychotic features.

**Clinical diagnosis**
The patient developed severe depressive symptoms with catatonia, psychotic symptoms, paranoid thoughts, nihilistic delusions and auditory hallucinations and so was admitted informally to a psychiatric ward. Examination was normal, with no abnormal neurological findings.

**Differential diagnosis**
Mood disorder, steroid-induced psychosis and other autoimmune encephalitides.

**Laboratory diagnosis**
Blood tests on admission revealed a raised erythrocyte sedimentation rate, white cell count (with neutrophilia), raised urea and creatinine and raised alanine transaminase (ALT) and Bilirubin. The serum sample sent on admission, which was available later, was low positive for anti-N-Methyl-D-Aspartate receptor (NMDAR) antibodies.

**Imaging diagnosis**
A computed tomography (CT) scan of the head did not demonstrate any abnormality. Magnetic resonance imaging of the head was normal. A CT scan sent on admission, which was available later, was low positive for anti-N-Methyl-D-Aspartate receptor (NMDAR) antibodies. A computed tomography (CT) scan of the head did not demonstrate any abnormality. Magnetic resonance imaging of the head was normal. A CT scan sent on admission, which was available later, was low positive for anti-N-Methyl-D-Aspartate receptor (NMDAR) antibodies.

**Treatment**
Multiple anti-depressants, benzodiazepines and anti-psychotics were initially trialled. She later received high dose steroids and plasmapheresis, followed by several sessions of electroconvulsive therapies (ECT).

**Related reports**
There are emerging case reports that demonstrate effective use of ECT in autoimmune encephalitis, either as an alternative or as adjunctive treatment with steroids and plasma exchange.

**Term explanation**
Anti-NMDAR encephalitis is the commonest of the autoimmune encephalitides. "Autoimmune encephalitides" represent conditions which may present with either psychiatric or neurological symptoms and require prompt and aggressive treatment (previously with steroids and plasmapheresis alone).

**Experiences and lessons**
It is important that the diagnosis is made swiftly so that the appropriate treatment can be commenced. ECT should be considered, particularly in those patients with psychiatric symptoms refractory to standard immunosuppressive therapies.

**Peer-review**
The authors make a great case advocating awareness for the disease, its diagnosis and treatment. This case report is a good contribution for treatment considerations.

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