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Catatonia in anti-NMDA receptor encephalitis: a case series and approach to improve outcomes with electroconvulsive therapy

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ABSTRACT

Background Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis has been recognised to present with the syndrome of catatonia. In severe cases dysautonomia is representative of malignant catatonia. The treatment with benzodiazepines (BZDs) and electroconvulsive therapy (ECT) may decrease morbidity and mortality in patients presenting with anti-NMDA receptor encephalitis and catatonia.

Methods This is a retrospective case series of eight patients with anti-NMDA receptor encephalitis treated with ECT. We use clinical prediction scores (Clinical Assessment Scale for Autoimmune Encephalitis [CASE] and anti-NMDAR Encephalitis One-Year Functional Status scores) to compare expected outcomes and observed outcomes.

Results CASE scores in our group ranged between 5 and 19, with a mean score of 13.8 (median 15.5). NEOS scores ranged from 2 to 4, with a mean and median of 3. Of the eight patients, six had a favourable modified Rankin Score (0–2) at a follow-up of 8 to 12 months. Patients received an average of 29.9 ECT treatments in total.

Conclusions Based on clinical prediction scores, this cohort had better than expected functional outcomes. We discuss the use of BZDs and ECT in these cases and propose a treatment algorithm for patients who present with catatonic syndrome in anti-NMDA receptor encephalitis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a limited evidence base to guide the management of symptoms of anti-N-methyl-D-aspartate (NMDA) receptor encephalitis beyond immunomodulation despite high morbidity and mortality.

WHAT THIS STUDY ADDS

⇒ This review of eight cases that received electroconvulsive therapy (ECT) for malignant catatonia due to anti-NMDA receptor encephalitis is the first to use clinical prediction scores to estimate the effects of ECT on patient outcomes, with patient outcomes being better than expected based on prediction scores.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Details of the treatments used, including specific ECT details and the timing of the intervention with respect to immunomodulation, are described to support future investigation, clinical practice and policy to increase the availability of ECT for this population.

INTRODUCTION

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a rare and potentially life-threatening autoimmune disorder of the central nervous system characterised by the production of antibodies targeting NMDA receptors within the brain, leading to neuronal dysfunction.[1–3] The clinical presentation involves a spectrum of neuropsychiatric symptoms, including movement disorders, seizures, status epilepticus and coma.[4–6] Psychiatric symptoms occur in 65% to 80% of cases and often precede neurological symptoms.[7–10] Among these symptoms, catatonia, a neuropsychiatric syndrome marked by behavioural and motor disturbances, poses a risk of long-term immobility and deconditioning[11] with severe manifestations of catatonia carry increased mortality risk.[6 12] Although first-line treatments with corticosteroids, intravenous immunoglobulin (IVIG) and plasmapheresis (PLEX) are the mainstay of treatment, persistent disease despite first-line therapy poses significant challenges and necessitates innovative approaches to further improve patient outcomes. In many cases, admission to an intensive care unit (ICU) is warranted for close monitoring, particularly in instances of refractory seizures and malignant catatonia, often complicated by severe dyskinesias, central hypoventilation and autonomic instability.[5] Current first- and second-line treatment strategies may result in slow treatment response, prompting the need for

additional interventions to enhance recovery, minimise morbidity and decrease mortality.

In addressing severe and malignant catatonia associated with anti-NMDAR encephalitis, recent literature highlights the potential efficacy of electroconvulsive therapy (ECT) as a viable option, providing faster recovery and shorter hospital stays.[6] While case reports and systematic reviews suggest promising outcomes, further research is essential to establish the extent and durability of its impact.

We share a series of eight cases of anti-NMDAR encephalitis treated with ECT, the first case series to include a comparison of expected outcomes and actual outcomes based on clinical prediction scores. We then propose a treatment algorithm that integrates benzodiazepines (BZDs) and ECT to manage catatonic symptoms alongside immunotherapy, emphasising the recognition of autonomic dysfunction as a manifestation of a catatonic syndrome.[5 6]

METHODS

A retrospective chart review was performed using patient data from the institution's Electronic Health Record. Patients with a diagnosis of autoimmune encephalitis (using International Classification of Diseases, Tenth Revision (ICD-10) codes for autoimmune encephalitis and related illnesses: G04.8, G04.81, G04.89, G04.9 and G04.90) who also received ECT (based on Current Procedural Terminology (CPT) code for the procedure) were identified. Chart abstraction was completed and reviewed by multiple authors. This study was approved by the Duke University Institutional Review Board (protocol number: Pro00110019).

Descriptive data were collected, including demographic information, initial presenting symptoms, initial Bush–Francis Catatonia Rating Scale (BFCRS) score, initial laboratory and imaging characteristics and immunotherapy received. All serum and spinal fluid anti-NMDAR antibody tests were performed via cell-based assay at Mayo Clinic Laboratories. Detailed data about ECT administration was recorded. Outcome measures, such as other procedural interventions, including tracheostomy and percutaneous endoscopic gastrostomy (PEG) tube placements, tumour removal, as well as ICU and hospital length of stay were also collected. Modified Rankin scale (mRS) scores were estimated at the time of discharge and after discharge. Clinical Assessment Scale for Autoimmune Encephalitis (CASE) scores, validated to assess the severity of autoimmune encephalitis,[13 14] were assigned retroactively via chart review by two independent reviewers (JK and NA) and adjudicated by a third reviewer (SS). Anti-NMDAR Encephalitis One-Year Functional Status (NEOS) scores[15] were assigned retroactively (JF) and reviewed by all authors. Descriptive statistics were performed on the data set. To assess the statistical significance of the difference between paired samples of the BFCRS, a two-tailed paired t-test was conducted using R software (version 4.4).

RESULTS

There were eight patients included in the study (case narratives in online supplemental appendix 1) of which seven patients were females, with a mean age of 26.4 years. Seizures were the most common presenting symptom (n=6), followed by psychosis (n=5). Mood symptoms (features of mania, including decreased need to sleep, increased energy, incessant laughing or emotional lability) were seen in four patients. Catatonia symptoms of mutism, stereotypy, echolalia and rigidity were seen in three of eight patients at presentation, though all developed symptoms of catatonia throughout their hospitalisation. Other common presenting symptoms were decreased appetite, headaches, agitation or aggressive behaviour. Ataxia and decreased levels of arousal were seen in one patient. Demographic data and presenting symptoms are outlined in table 1. All patients, except one, required admission to the ICU. CASE scores in our group ranged between 5 and 19, with a mean score of 13.8 (median, 15.5). NEOS scores ranged from 2 to 4, with a mean and median of 3.

Brain MRI abnormalities were seen in two patients: diffusion restriction and T2 signal hyperintensity in the right hippocampus without associated enhancement in one patient, while the other demonstrated restricted diffusion in the left insula and left frontal operculum in a study done without contrast. All patients had EEG abnormalities—five patients had seizures captured on EEG, while six patients had epileptiform discharges; six out of eight had diffuse generalised slowing. Delta brush was noted on the EEG restudies of two patients. A total of 10 lumbar punctures were completed (two patients had repeat studies); CSF pleocytosis was seen in 90% of the CSF samples, all of which were lymphocytic predominant, with a mean CSF white blood cell count of 52.2 cells/µL. CSF protein was rarely elevated, only seen in one of the 10 samples; the mean CSF protein was 29 mg/dL. Seven of eight cases had confirmed CSF anti-NMDAR antibodies. Case 3 had CSF anti-NMDAR testing confirmed positive at another hospital, though we were unable to obtain the titre results. For Case 8, CSF antibody testing results were not available. Further details about the laboratory and other objective data are shown in table 1.

The initial treatment included high-dose intravenous corticosteroids and IVIG for all eight patients, with treatment initiation occurring between hospital days 2 to 11. Two of these patients underwent a second course of IVIG during their hospitalisations. In addition, three patients underwent PLEX, and one patient received cyclophosphamide. Longer-term immunotherapy with rituximab was given to seven patients, and one patient also received tocilizumab. Three patients received long-term oral corticosteroids. Three patients were found to have ovarian teratomas, which were resected between hospital days 3

Table 1 Demographic data

	Total 8 patients	
	Number	**%**
Age		
Mean	26.4 years	
Median	24 years	
Sex		
Male	1	12.5%
Female	7	87.5%
Presenting symptoms		
Seizures	6	75.0%
Psychosis	5	62.5%
Catatonia	3	37.5%
Decreased appetite	3	37.5%
Insomnia	2	25.0%
Headaches	3	37.5%
Agitation/aggressive behaviour	3	37.5%
Other psychiatric symptoms*	4	50.0%
Other neurologic symptoms†	1	12.5%
CSF abnormalities (n=10 lumbar punctures)		
Pleocytosis	9	90%
Lymphocytic predominance	10	100%
Mean CSF WBC count	52.2	
Elevated protein	1	10%
Mean CSF protein	29.4	
MRI abnormalities	2	25%
EEG abnormalities	8	100%
Initial BFCRS		
Mean	22.4	
Median	23	
CASE scores at the time of ECT initiation		
Mean	13.75	
Median	15.5	
NEOS scores		
Mean	3	
Median	3	

*Other psychiatric symptoms: including mania, emotional lability
†Other neurologic symptoms: including ataxia, decreased level of arousal
BFCRS, Bush–Francis Catatonia Rating Scale; CASE, clinical assessment scale in autoimmune encephalitis; CSF, cerebrospinal fluid; ECT, electroconvulsive therapy; NEOS, anti-NMDAR Encephalitis One-Year Functional Status score.

and 14; no other tumour type was found in this patient cohort. Details of case presentations and immunotherapy are outlined in table 2.

All patients in this series developed malignant catatonia during their admission, with autonomic instability. Their mean initial BFCRS score was 22.1 (median 22.5). BZDs were challenged and continued if patients had any clinical response; lorazepam was used as the initial treatment, ranging from 24 mg to 156 mg daily dose at the peak dose. Patients received an average of 29.9 ECT treatments in total (including index and maintenance treatments). Details of ECT treatment are outlined in table 3. Seven of eight patients started ECT in the ICU setting, with all non-ICU treatments occurring in a dedicated ECT suite. None of the patients were admitted to a psychiatric unit at any point during their treatment course.

There were no acute adverse events associated with ECT noted in the medical record or on chart review. Two of eight patients (case #6 and case #7) exhibited seizures after ECT initiation, and both patients were among the six patients with confirmed seizures before the ECT initiation. Cognitive adverse effects of ECT were not measured due to the severity of catatonia exhibited by all patients.

Outcome details are outlined in table 4. The mean reduction in BFCRS score for all patients was 18.5 points (95% CI [12.6, 24.4]). Seven of eight patients required intensive care, with four patients requiring mechanical ventilation and three underwent tracheostomy placement. The mean ICU length of stay was 47.4 days (median 42.5). The total hospital length of stay ranged from 62 to 137 days; however, seven patients were discharged to either home or acute inpatient rehab, and no patients were discharged to skilled nursing facilities or long-term acute care hospitals. One patient (#6) expired during hospitalisation (details in online supplemental appendix 1). Two cases, #2 and #6, did not appear to benefit from ECT. Case #2 demonstrated short seizures (6 of 11 treatments with a seizure duration <20 s). In the remaining patients, the mRS scores at discharge were favourable (mRS 0–2) in two patients, though the other five patients were mRS 3 (ambulatory but needed assistance with ADLs). At 1 year, six out of seven living patients had a favourable mRS 0–2, while one patient was lost to follow-up. See figure 1 for the breakdown of mRS scores at discharge, at follow-up between 3–6 months after the onset of symptoms and at around 8–12 months after the onset of symptoms.

DISCUSSION

Several previous case reports and systematic literature reviews have described patients with malignant catatonia related to anti-NMDAR encephalitis who showed significant improvement following the addition of ECT to treatment regimens.[4–6] Although these studies are limited by their small sample size and lack of control groups, these reports suggest that ECT with BZDs may facilitate faster recovery by preventing progression of catatonia, dysautonomia and psychotic features, potentially improving neurological, cognitive and functional outcomes. The extent of these improvements and their long-term sustainability requires further investigation.

We describe here eight cases of anti-NMDAR encephalitis in which ECT was used to target symptoms of catatonia at various stages of illness. Five of the eight patients

Table 2 Detailed case presentations

	Cases							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Initial presenting symptoms	Psychosis, seizure	Psychosis, seizure	Psychosis	Seizure	Psychosis	Seizure	Anxiety	Seizure
Initial CASE score	17	14	7	19	17	15	5	16
NEOS Score	4	2	2	4	3	4	3	2
EEG abnormalities								
Generalised slowing	+	–	–	+	+	+	+	+
Focal slowing	Left frontal	Left	–	–	–	Right	–	–
Epileptiform discharges	Right temporal	Left temporal	Bilateral frontal	–	–	Right	Left temporal	Left temporal
Seizures	Right temporal	Left temporal	–	–	–	Right	Left temporal	Right/Left temporal
Delta brush	–	–	–	–	+	+	–	–
MRI abnormalities	+	–	–	–	–	+	–	–
CSF pleocytosis								
CSF WBC count	41	80	13	62	26	49, 67	78, 91	3
Predominant cell type	96% lymph	78% lymph	100% lymph	88% lymph	95% lymph	89, 96% lymph	95, 98% lymph	97% lymph
CSF protein	32 (normal)	23 (normal)	33 (normal)	18 (normal)	18 (normal)	56 (high)	22 (normal)	27 (normal)
Initial antibody titre								
CSF	1:160	1:32	+	+	1:128	>1:1024	1:64	n/a*
Serum	1:80	–	+	+	–	–	–	<1:240
Immunotherapy								
Hospital day of the first immunotherapy	2	8	3	7	11	8	2	3
IV steroids	+	+	+	+	+	+	+	+
IV immunoglobulin	+	+	+	+	+	+	+	+
Plasmapheresis	+	–	+	–	–	+	–	–
Second-line immunotherapy	–	Rituximab	Rituximab	Cyclophos-phamide, rituximab, prednisone	Rituximab	Rituximab, tocilizumab, prednisone	Rituximab	Rituximab
Tumour								
Type	Ovarian teratoma	–	–	–	Ovarian teratoma	–	Ovarian teratoma	–
Removed	Yes				Yes		Yes	
HD of tumour removal	10				14		3	
*n/a=not assessed								

*n/a=not assessed
CASE, clinical assessment scale in autoimmune encephalitis; CSF, cerebrospinal fluid; NEOS, anti-NMDAR Encephalitis One-Year Functional Status; WBC, white blood cell.

Table 3 Electroconvulsive therapy and outcomes by cases

	Cases							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Initial BFCRS score	21	22	11	30	25	25	23	20
Latest BFCRS score	0	9	1	0	0	14	2	3
Peak lorazepam dose (per day)	59 mg	24 mg	61 mg	74 mg	82 mg	152 mg	69 mg	104 mg
HD of peak dose	32	24	7	84	33	107	11	27
ECT*								
HD of first ECT	26	30	18	68	19	46	4	16
ECT total index	16	11	27	24	34	27	36	48
ECT maintenance	0	0	11	0	3	0	2	0
Max charge/protocol step†	Step 7 (376 mC)	Step 8 (576 mC) 35 Hz / 0.9 amps	Step 8 (576 mC)	Step 8 (576 mC)	Step 8 (576 mC)	Step 8 (576 mC)	Step 8 (576 mC)	Step 8 (576 mC)
Electrode placement	Bitemporal	Bitemporal	Bitemporal	Bitemporal	Bitemporal	Bitemporal	Bitemporal	Bitemporal
Flumazenil dose	1 mg to 2 mg	0.5 mg to 1 mg	1 mg to 2 mg	1 mg to 2 mg	0.5 mg to 2 mg	2 mg to 3 mg	1 mg to 2 mg	1 mg to 3 mg
Medical interventions								
Tracheostomy	–	–	–	+	–	+	+	–
PEG	–	–	–	+	–	+	+	–
Tracheostomy decannulated prior to discharge				Yes		No	Yes	
ICU LOS	19	0	42	63	43	128	67	17
Hospital LOS	62	73	75	123	72	137	72	136
Discharge location	Acute rehab	Home	Home	Acute rehab	Acute rehab	Deceased	Acute rehab	Home
mRS at discharge	2	3	2	3	3	6	3	3
mRS at 3–6 months	1	1	2	3	3	6	3	3
mRS at 8–12 months	1	0	1	–	0	6	2	2

Note: three of the above cases were previously reported[40]
*Electroconvulsive therapy performed using a MECTA Spectrum or Sigma device, 1.0 msec pulse width and 0.8 Amp current (unless noted).
†Stimulus threshold determination performed in all cases at the first treatment, with the subsequent therapeutic dose administered at two times the seizure threshold according to institutional protocol, with additional dose adjustments based on seizure duration and clinical response.
BFCRS, Bush–Francis Catatonia Rating Scale; ECT, electroconvulsive therapy; HD, hospital day; ICU, intensive care unit; LOS, length of stay; mC, millicoulombs; mRS, modified Rankin Score; PEG, percutaneous endoscopic gastrostomy.

Table 4 Treatments and outcomes

	Total eight patients	
	Number	**%**
Immunotherapy		
Solumedrol	8	100.0%
Intravenous immunoglobulin	8	100.0%
Plasmapheresis	3	37.5%
Cyclophosphamide	1	12.5%
Rituximab	7	87.5%
Steroid taper	3	37.5%
Tracheostomy placed	3	37.5%
Intensive care length of stay		
Mean	47.4 days	
Median	42.5 days	
Hospital length of stay		
Mean	93.8 days	
Median	74 days	
Discharge location		
Home	3	37.5%
Acute rehab facility	4	50.0%
Skilled nursing facility	0	0.0%
Long term acute care hospital	0	0.0%
Deceased	1	12.5%
Change in BFCRS score change		
Mean reduction	18.5 points*	
Good functional outcome (mRS 0–2)		
At discharge	2	25.0%
3–6 months after the onset	3	37.5%
8–12 months after the onset	5	62.5%

*(95% CI [12.6, 24.4])
BFCRS, Bush–Francis Catatonia Rating Scale.

received ECT early during illness presentation due to rapid development and early recognition of the syndrome of malignant catatonia, while three patients were treated later in their course. Prompt recognition and treatment of catatonia were central to the improvement in outcomes noted in many of these patients. Given the morbidity and mortality that can be associated with malignant catatonia and the sequelae of prolonged ICU stay,[16 17] this data suggests that ECT may have provided benefit to decrease morbidity as an adjuvant to immunotherapy in patients exhibiting symptoms of malignant catatonia.

Two clinical outcome scales, the CASE score and the NEOS score, were retrospectively applied to estimate the expected functional status in this case series. The patients in this cohort were categorised as ill at presentation, defined by a mean CASE score of 13.8, which is associated with a low probability of good functional outcome.[13] Additionally, the mean NEOS score of 3 is associated with approximately 50% probability of a good functional outcome, as defined by mRS of 0–2.[15] However, at 8–12 months following presentation and treatment with ECT, six of eight patients in this cohort had improved to a good functional outcome (mRS of 0–2). The addition of ECT may have contributed to this relative improvement of functional outcomes compared with the expected prognosis by initial scores; the other two patients included one death due to complications of prolonged illness and ICU stay, and one patient was lost to follow-up.

Previous case reports have included limited details on the ECT treatment protocols,[16] but it appears that our average number of 29.9 treatments in this case series is higher than other reports.[6] This may be due to the early initiation of ECT in some of our cohort during the period of ongoing inflammation, which may be supported by longer ECT course in other cases of autoimmune central nervous system (CNS) disease causing catatonia.[18] While the standard cadence of ECT is typically two to three

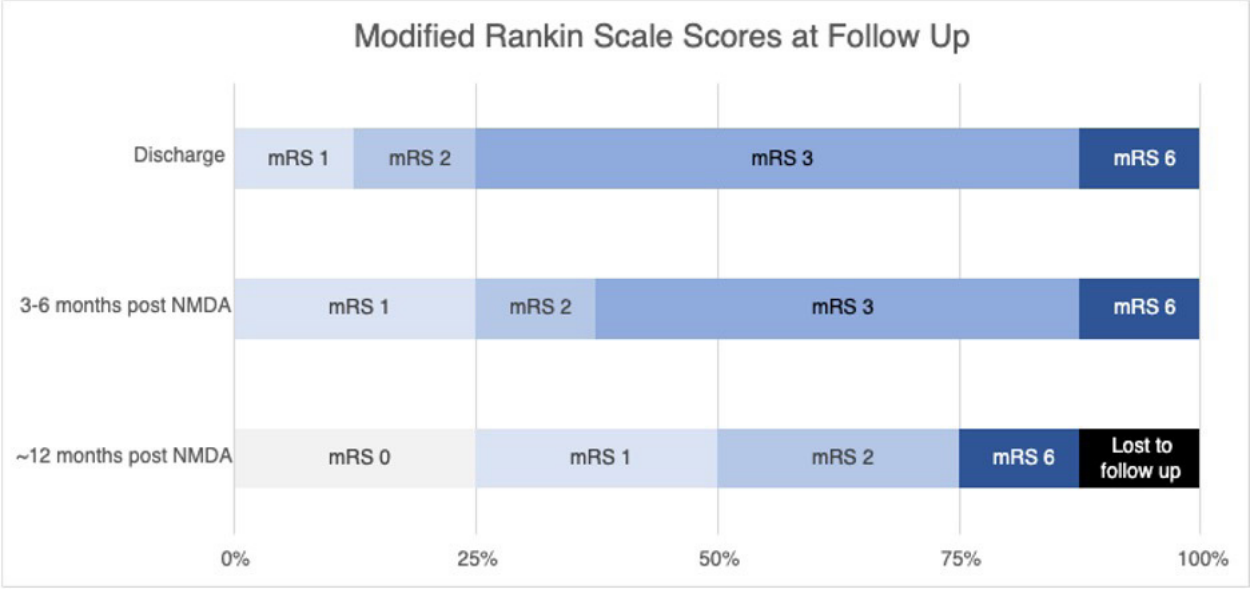

Figure 1 Modified Rankin scale scores at follow-up (include colour in graphic).

treatments per week for a total of 6–12 treatments for psychiatric disorders,[19] daily ECT (used in case #6 and #7), also known as en bloc ECT,[20] has been described in malignant catatonia and the related neuroleptic malignant syndrome.[20–23] The primary risk for increased ECT frequency is cognitive worsening,[24] though this must be weighed against the morbidity and mortality of severe catatonia. The use of multiple ECT stimuli in a single session is described with benefit in the practice of multiple monitored ECT (mmECT).[20] The American Psychiatric Association guidelines indicate mmECT can be considered in the setting of neuroleptic malignant syndrome, which is now considered in the same spectrum as malignant catatonia.[17] Our use of two ECT treatments separated in time in a single day (case # 5) differs from mmECT in that a new administration of anaesthesia is required at a later time point; however, the risks should be comparable. We observed marked but non-sustained benefit in dysautonomia in this case with daily treatments, which prompted the second daily treatment. Future investigation is needed regarding the risks and benefits of this approach.

Two cases, #2 and #6, did not appear to benefit from ECT. Case #2 demonstrated short seizures during ECT, which raises the question of inadequate ECT, as consensus guidelines state that short seizures may indicate inadequate ECT.[25] Case #6 exhibited refractory dysautonomia and status epilepticus that did not respond to any therapy, except continuous propofol infusion. It was unclear what factors contributed to the severity and refractoriness of this patient's illness, an area in need of future research.

The mechanism of catatonia has several molecular hypotheses, including dysfunctions in dopamine, gamma-aminobutyric acid and glutamate systems, including NMDA receptor dysfunction.[5] Catatonia carries a significant risk for medical complications secondary to malnutrition and immobility, including venous thromboembolism, pressure injury and infection, as well as the risk of progression to malignant catatonia, a condition characterised by autonomic instability, which is associated with increased mortality.[16 26] This carries particular importance in anti-NMDAR encephalitis, with 42–70% of patients presenting with catatonia.[6 16 27] In this cohort, we diagnosed catatonia primarily after the identification of dysautonomia, which changed our management by prompting earlier initiation of ECT. Several theories on ECT's therapeutic mechanism of the effect have been postulated, with an overall enhanced GABAergic response within the CNS, leading to an anti-catatonic effect.[4] The use of BZDs and ECT is suspected to be synergistic,[5 28] which aligns with this case series in which all patients had partial benefit from high-dose BZDs which were continued during the ECT course. Another hypothesised mechanism of ECT includes upregulation of NMDA receptors,[5] which may be specifically relevant in anti-NMDA receptor encephalitis.

Though there is a theoretical concern regarding ECT seizure induction in the setting of active encephalitis, there is evidence that ECT may have a neuroimmune effect via microglial cell regulation in the CNS[29] and ECT has been used safely in other neuroimmunological processes.[30] Additionally, there have been reported cases of anti-NMDAR encephalitis that responded to ECT without immunomodulatory therapies.[7 16]

While there were two instances of spontaneous seizure following the ECT initiation in our cohort, we note that six of eight patients had EEG confirmed seizures or epileptiform discharges before the ECT initiation and ECT was administered concurrently with antiepileptics. Case #7 had a single clinical seizure event after ECT start, and none subsequently. Case #6 demonstrated status epilepticus before the ECT initiation and again during ECT course prompting ECT cessation. ECT has been used as a treatment for seizure disorders and status epilepticus, with a hypothesised antiepileptic effect via the increase in gamma aminobutyric acid mediated inhibition of action potential propagation, thus elevating seizure threshold post-treatment.[31] ECT can be safe and effective in the setting of seizure disorder and antiepileptic medications.[32 33] It was noted that given the concurrent use of high-dose BZDs in all eight of these cases, flumazenil was administered 2 min before the ECT stimulus to reverse the BZD effect on seizure threshold without evidence of long-term sequelae. We followed consensus practice to administer a dose of intravenous BZD immediately following ECT seizure termination to minimise withdrawal effects from flumazenil. The safety and efficacy of flumazenil use in ECT has been described.[34]

While the adverse cognitive side effects of ECT are well described,[35] all patients in this cohort demonstrated features of catatonia (ie, mutism, withdrawal) that prevented serial assessments of cognition. Additionally, anti-NMDAR encephalitis is known to result in cognitive deficits,[36] and so differentiating illness effects from ECT side effects is a challenge. We hypothesise that proper identification and treatment of catatonia with ECT may support cognitive recovery in these patients, as has been described in catatonic illness.[37] Further study is needed regarding the cognitive trajectory of patients with this condition, with and without the use of ECT.

A recent scoping review (39 cases) and retrospective cohort study (21 cases) by Wright *et al* gathered observational data of outcomes among anti-NMDAR encephalitis patients that received ECT. While the authors conclude that there is a lack of evidence to support the use of ECT in this condition, they reported a high proportion of patients receiving ECT before immunotherapy (46% in the scoping review and 69% in the retrospective review).[38] Notably, 100% of the patients in our cohort received prompt first-line immunotherapy before ECT (table 2, see table 3 to compare ECT initiation timing), and six of eight patients escalated to second-line immunotherapy. This difference emphasises the current expert opinion[39] (figure 2) that the use of ECT is adjunctive to immunotherapy when the syndrome of catatonia, particularly with dysautonomia, is present and contributing to short-term risk for morbidity or mortality. These retrospective reviews are limited in their ability to establish causal relationships, yet the outcomes among patients that received ECT after immune

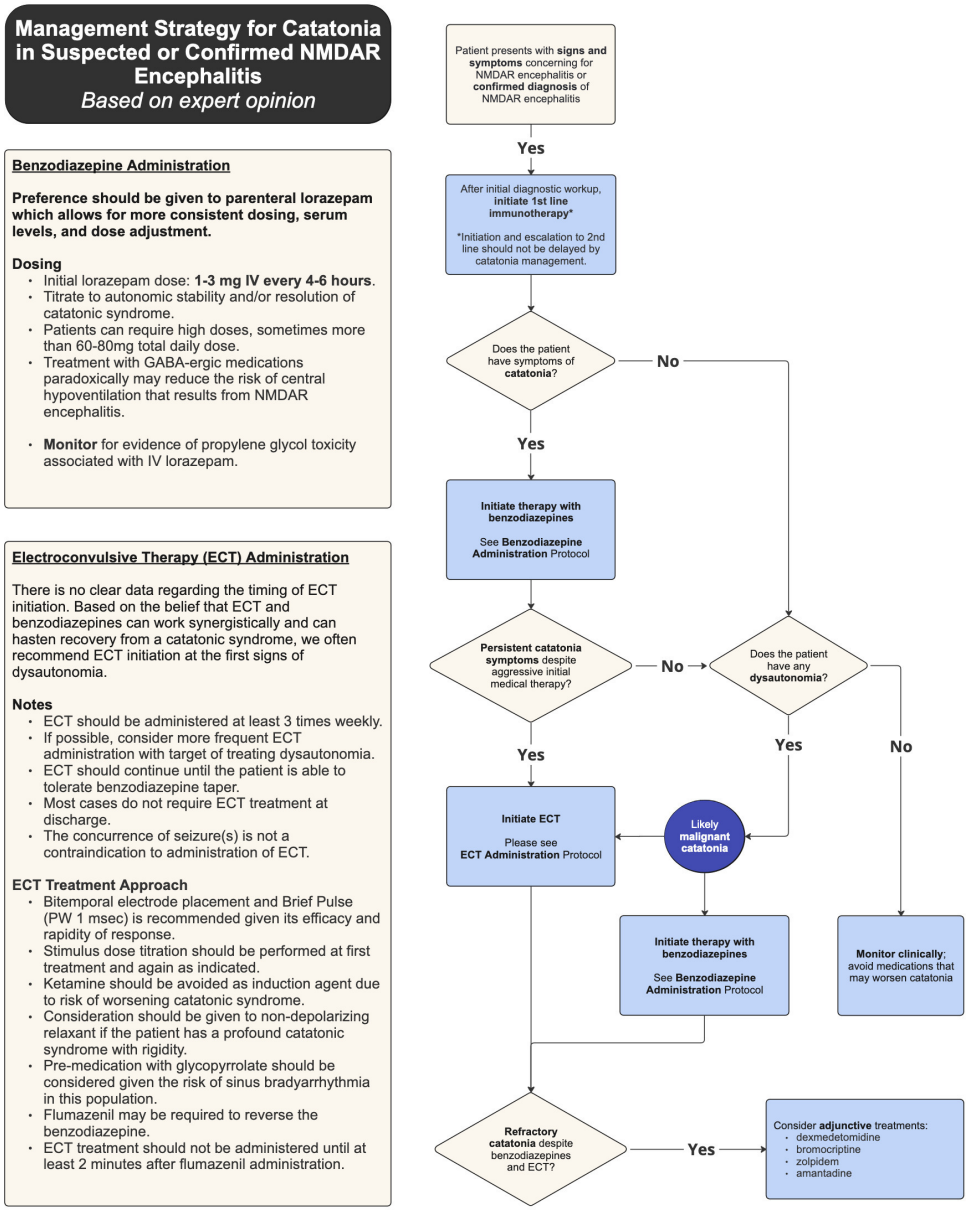

Figure 2 Management of suspected or confirmed encephalitis (include colour in graphic).

therapy in the Wright cohort[39] and in our cohort indicate that the approach warrants additional prospective study.

This case series has multiple limitations including a small sample size owing to the rarity of the disease. Given that chart review was done retrospectively, functional status scoring (CASE, NEOS, mRS) could be susceptible to recall and observer bias. This was mitigated by having two blinded reviewers independently score each case, with differences adjudicated by a third senior reviewer. Patients with this severity of catatonia tend to receive ECT at this institution, meaning a control group cannot be identified and asserting causation is not possible. This cohort only includes patients from a single hospital system, which could introduce a selection bias with regard to patient demographics and treatment approach. However, the standard of care was followed; second-line therapies and ECT were only initiated when the clinical response to first-line therapies was inadequate. Larger, prospective, multi-centre studies are needed to further define the impact of ECT on clinical outcomes in anti-NMDAR encephalitis.

In summary, this case series found that the treatment of malignant catatonia with ECT in patients with anti-NMDAR encephalitis was safe and positively affected patient outcomes. We propose a treatment algorithm that highlights a multidisciplinary approach to anti-NMDAR encephalitis (figure 2) and provides a pathway for the management of catatonia in these patients that may be unresponsive to first-line immunotherapy, emphasising that dysautonomia may be a sign of malignant catatonia. Further research is needed to better understand the underlying mechanisms and to optimise the use of ECT in the management of catatonia associated with anti-NMDAR encephalitis.

Contributors JF is the guarantor and contributed to conceptualisation, writing, analysis and revision. FGK contributed to conceptualisation and initial draft. DTM contributed to chart review and writing. RDS contributed to chart review and writing. NA contributed to conceptualisation, chart review, table creation and revision. SS, CE and JRK contributed to conceptualisation and revisions.

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