Case Report

Ketamine use in refractory status epilepticus associated with anti-NMDA receptor antibody encephalitis

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Abstract

Purpose: Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDAr encephalitis) is an auto-immune disorder associated with the production of antibodies against NR1 and NR2 sub-units of the NMDA receptor. Seizures in this population are reported in up to 50% of cases with status epilepticus being reported in 25% of cases, refractory status epilepticus in 13.8% of cases and super-refractory status epilepticus in 10.2% of cases. Treatment of refractory epileptic activity in this population is not uniform and heterogeneous.

Methods: We present three cases of super refractory status epilepticus in patients with anti-NMDAr encephalitis treated successfully with ketamine, a noncompetitive NMDA receptor antagonist. All patients had failed to improve clinically on multiple anti-convulsants and immunotherapy prior to initiation of ketamine therapy.

Results: In all three cases, administration of a load followed by maintenance infusion (0.05 mg/kg/min infusion) of ketamine yielded clinical and/or electrographic seizure cessation in less than 48 h. Patients were treated for a heterogeneous duration although ultimately, epilepsy outcomes were favorable from a seizure freedom standpoint. Earlier treatments with ketamine were associated with better epilepsy outcomes in this case series.

Conclusion: Ketamine may be a useful adjunct treatment in super-refractory status epilepticus in patients with NMDAr encephalitis.

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1. Introduction

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDAr encephalitis) is an auto-immune disorder associated with the production of antibodies against NR1 and NR2 sub-units of the NMDA receptor, originally described by Dalmau et al. in 2008 [1]. Clinical manifestations include neuropsychiatric changes, amnesia, dyskinesia, and seizures [2]. This latter association is unsurprising given the epileptogenic potential of the NMDA receptor [3]. Seizures in this population are reported in up to 50% of cases with status epilepticus (SE) being reported in 25% of cases, refractory SE (RSE) in 13.8% of cases and super-refractory SE (SRSE) in 10.2% of cases [2,4].

There exist no specific treatment recommendations for seizures or SE in patients with anti-NMDAr encephalitis. Ketamine, a competitive NMDA receptor antagonist, has been previously used to treat SE, RSE, and SRSE [5,6]. While the primary pathology of anti-NMDAr encephalitis takes place at the NMDA receptor, there have been no studies identifying the utility of this agent in preventing seizures persons with anti-NMDAr encephalitis. This case series reports three patients with anti-NMDAr encephalitis and RSE treated with ketamine.

2. Case 1

An otherwise healthy, 3-year-old male, presented with sub-acute somnolence, irritability, and decreased verbal output and clustering of seizures, one week after having a first-time seizure. Clinical features, imaging, lab work up, and treatment are displayed in Table 1. Following development of seizures 8 days after diagnosis, the patient was treated multiple anti-convulsants (AEDs) with minimal effect (Table 1). Ketogenic diet was initiated four days after the development of SE but given acute worsening, ketamine was administered by IV (40 mg load followed by 3 mg/kg/h infusion) 24 h after the start of the ketogenic diet (although the patient was not yet in ketosis).

Within 12 h, the patient’s EEG demonstrated a dramatic reduction in sub-clinical seizure activity by 80%. Within 48 h, the patient’s EEG reflected a decrease in multi-focal sharp activity, delta brushes, and displayed normalization of sleep/wake patterns and A/P gradient. Clinically, the patient became less encephalopathic during this time but continued to suffer from prominent dystonia/dyskinesia and dysautonomia.
The patient was able to be weaned off ketamine after 3 weeks and was discharged with no further seizures. The patient was seizure free on levetiracetam monotherapy at one year and has made a full recovery from NMDAr encephalitis.

3. Case 2

A 19-year-old female presented with intermittent amnesia, emotional lability, aggression, and impulsivity following return to university. Clinical features, imaging, lab work up, and treatment are displayed in Table 1. On hospital day 5 the patient had a 30-second generalized seizure. EEG at that time demonstrated left temporal slowing and rare sharp waves at the T4 lead and she was treated with levetiracetam.

Two weeks in to hospitalization, the patient had a cluster of seizure activity progressing over 24 h to non-convulsive SE. The patient was aggressively treated with anticonvulsants (Table 1). She continued to have frequent sub-clinical seizure activity up to 2–3 times per hour on this regimen. Six days after onset of SE the patient received a loading dose of 50 mg of ketamine followed by an infusion of 3 mg/kg/h. Within 2 days of this regimen, Six days after onset of SE the patient received a loading dose of 50 mg of ketamine followed by an infusion of 3 mg/kg/h. Within 24 h, the patient had no seizure activity. Her mental status continued to be difficult to determine given severe catatonia, but EEG recordings demonstrated no breakthrough seizure activity. The patient was titrated off ketamine, phenobarbital and phenytoin over three weeks and was continued on a combination of lacosamide, levetiracetam and valproic acid.

This patient had no further seizure activity but continued to have neurologic sequelae 6 months after diagnosis. A second dose of rituximab was administered at that time as was repeat IVIg (2 g/kg over 5 days) and IV methylprednisolone (1 g/kg x 5 days). The patient continues to have neuropsychiatric disease and is unable to work but has no further seizure activity on two AEDs.

4. Case 3

A 54-year-old female with no past medical history presented with subacute alterations in mental status consisting of progressive encephalopathy, amnesia, and developed stereotyped movements. Clinical features, imaging, lab work up, and treatment are displayed in Table 1. The patient developed generalized convulsions on hospital day 12...

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**Table 1**

Clinical and electrographic data from cases.

| Case 1 | Case 2 | Case 3 |
|--------|--------|--------|
| Age | 3 years, 6 months | 19 years, 2 months | 54 years, 2 months |
| Sex | Male | Female | Female |
| Days to diagnosis | 10 days | 28 days | 14 days |
| Clinical symptoms* | Encephalopathy | Movement Disorder | Dysautonomia |
| Initial Lumbar Puncture | WBC: 38 cells/μL | % Lymphocytes: 78 | Total Protein: 55 mg/dL |
| Immunomodulatory treatments | IVIg (2 g/kg over 5 days) x 1 | IV methylprednisolone (30 mg/kg/d x 5 days) x 1 | Rituximab x 1 |
| Time from diagnosis to 1st Seizure | 8 days | – | – |
| Seizure Semiology | Generalized convulsion without aura. | Focal motor seizure with Jacksonian march | Focal motor seizure with Jacksonian march |
| AEDs utilized | Levetiracetam, Valproic Acid, Clobazam | Levetiracetam, Valproic Acid, Clobazam | Levetiracetam, Valproic Acid, Phenytoin |
| Anti-NMDAr antibody titer at diagnosis (CSF) | 1:1280 | 1:2560 | 1:1280 |
| Initial MRI Brain | Normal | Normal | Normal |
| Neoplasia | No | No | Ovarian Teratoma |
| Time from diagnosis to 1st Seizure | 27 days (day 35) | 15 days (day 20) | 94 days (day 106) |
| Non-convulsive SE? | No | Yes | Yes |
| Seizure onset localization on EEG | Left temporal | Multi-focal (right temporal and left fronto-temporal) | Right fronto-temporal |
| Time from SE to ketamine | 9 days (day 44) | 4 days (day 24) | 32 days (day 138) |
| Days to improve clinically or electrographically after ketamine | <1 day (day 45) | 1 day (day 25) | 2 days (day 40) |
| Seizures after ketamine use | 0 seizures in 24 h | 0 seizures in 24 h | 0 seizures in 48 h |
| Anti-epileptics at 12 months | Yes: Levetiracetam | Yes: Levetiracetam and Valproic acid | Patient Expired |
| Symptoms at 12 months | No | Yes: neuropsychiatric only | Patient Expired |

Legend: g/kg: grams per kilogram; IVIg: intravenous immunoglobulin; MRI: magnetic resonance imaging; RBC: red blood cell count; WBC: white blood cell count.

* Within 4 weeks of diagnosis.
which were initially responsive to levetiracetam. Given the patient’s continued encephalopathy and movement disorder, she was continued on monthly infusions of rituximab during this time.

On hospital day 94, the patient developed acute deterioration in mental status and was found to be in non-convulsive SE. Multiple AEDs were ineffective in treating her SE which progressed to SRSE. Ketamine was administered by IV (40 mg load followed by 3 mg/kg/h infusion) 24 h over a month after the onset of SRSE. Within 48 h, all patient stopped seizing. Over the span of 14 days, the patient was slowly titrated off ketamine, but was maintained on all other AEDs.

The patient had an unexpected cardiac arrest while hospitalized in the ICU which caused significant anoxic brain injury. Due to her poor prognosis from two neurologic insults, care was withdrawn.

5. Discussion

Although infrequent in patients with anti-NMDAr encephalitis, medically refractory epilepsy and SE can be challenging when encountered. The cases reported describe improvements in seizure activity with the addition of ketamine to RSE and SRSE therapy providing a potential tool to consider in the management of these patients with an acceptable safety profile [7]. The authors note that early administration of ketamine in the course of RSE and SRSE had the most dramatic effect on both seizure activity.

The pharmacology of status epilepticus is complex, especially with regard to the deleterious effects caused by and affecting the NMDA receptor. While down regulation of synaptic GABA(a) receptors and up regulation of synaptic NMDA receptors are observed in prolonged seizure activity, management of SE only targets half of the issue [8,9].

It is unsurprising that epilepsy literature has demonstrated therapeutic effects of ketamine in SE, RSE, and SRSE [4,10].

The unanswered, and seemingly counterintuitive, issue of how the use of an NMDAR antagonist in a disease state shown to cause blockade and internalization of the same receptor remains. There are no studies that have interrogated this question directly although hypotheses have been proposed. Ketamine is known to have a variety of effects on other receptors (opioid μ, κ, and δ; GABA-A, muscarinic and nicotinic acetylcholine receptors, D2 and Toll-like receptor 4), reuptake systems (serotonin, norepinephrine, dopamine and GABA), enzymatic production of nitrous oxide, and potentially epigenetic changes. It is unclear if any or all of these pathways improve epilepsy outcomes although downstream effects may provide a mechanism for the anti-convulsive properties of ketamine in NMDA receptor [6,9,11]. There is data to support the role of ketamine as an anti-inflammatory agent beyond its neuroprotective effects on decreasing hyperexcitability with potential effects on transcription activator protein-1, nuclear factor-κB, interleukin-6, and tumor necrosis factor α [12]. As SE, RSE, and SRSE are all considered inflammatory, these less studied mechanisms of action of ketamine may be contributory to its anti-convulsant properties. Finally, it is also possible that ketamine provides a blockade for insult at the NMDA receptor, preventing internalization of the receptor complex, although this is thought to be less likely in the setting of ketamine’s non-competitive pharmacodynamics.

Acute management of seizures in patients with anti-NMDAr encephalitis is clear although the timeframe with which to use agents like ketamine is unknown. The majority of patients with anti-NMDAr encephalitis that do have seizures during their acute course generally have good epilepsy outcomes with one study by Liu et al.; with 80% of patients with anti-NMDAr encephalitis and seizures having no additional seizures six months after diagnosis [4]. This same study also noted no difference in long-term epilepsy outcomes in patients receiving short term (<3 months) or long term (≥3 months) AED therapy, even amongst patients with SE, RSE and SRSE which may indicate that immunotherapy and aggressive acute management may be potent drivers in optimizing epilepsy and symptomatic outcomes in this population.

| Time (days) Between IVlg and … | Case 1 | Case 2 | Case 3 |
|--------------------------------|--------|--------|--------|
| 1st Seizure                    | 7      | 11     |        |
| Refractory SE                  | 34     | 14     |        |
| Ketamine Infusion              | 43     | 18     |        |
| Discontinuation of SE          | 44     | 19     |        |
| Time (days) Between 1st Infusion of Rizutimab and 1st Seizure | n/a | n/a | n/a |
| Refractory SE                  | 21     | 10     |        |
| Ketamine Infusion              | 30     | 14     |        |
| Discontinuation of SE          | 31     | 15     |        |
| Time (days) between CD19/20% at 0 and Ketamine use … | 19 | 7 | 120 |

As this is a retrospective case series, there are multiple limitations to the report of these results. The authors present three very heterogeneous cases of anti-NMDAr encephalitis [1,2]. Additionally, the therapeutic intervention used, while standardized in terms of dosing, was administered at different time points in the clinical course of the patients. It is difficult to fully isolate the effects of ketamine from both existent AED therapy and immunotherapy although improvement occurred in all cases after other therapies had failed to alter the clinical course (Table 2). Finally, the age of the patients may be difficult to make strong inferences from as they represent the extremes of persons acquiring anti-NMDAr encephalitis.

Ethical statement

Drs. Santoro, Filippakis, and Chitnis report that they have conformed to the principles of ethics in publishing and ethical guidelines for journal publication, as referenced by Epilepsy and Behavior Case Reports.

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