ECT for Anti-NMDA receptor encephalitis: a systematic review of cases

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About me

• Second year trainee, at beginning of stage 2
• Project undertaken during my consultation liaison term: February – August 2018
• Project supervisor - consultation liaison psychiatry consultant Dr Nicola Warren
Outline

• What is NMDA receptor
• What is anti-NMDA receptor encephalitis
• Treatment
• Our aim
• Methods
• Results
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• Limitations
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• Acknowledgements
NMDA Receptor
Anti-NMDAR binding/crosslinking

Internalisation

Dysfunctional synapse
NMDAR encephalitis

- NMDAR encephalitis continues to be of interest since identification in 2007
- Syndrome classically consists of:
  - psychiatric disturbance (often severe) behavioral disturbance, mood disorder, psychosis & catatonia
  - movement disorders,
  - seizures and
  - autonomic instability
- It is more common in young females, &
- Associated with ovarian teratoma or other malignancies in around 50% cases
NMDAR encephalitis
NMDA R encephalitis

- Progression of disorder & development of neurological symptoms & autonomic disturbance, often requires intensive care admission & lengthy hospitalisation.
- Tumour removal & immunomodulatory therapy are the standard treatments.
- Rate & nature of deterioration from psychiatric symptoms is variable, & there is often a delay before CSF antibody confirmation of the disorder; thus an initial primary psychiatric diagnosis of mania or psychosis is common.
NMDA R Encephalitis

Psychiatric

Movement

Seizures

Autonomic

(Dalmau 2011)
Treatment

• Although primary treatment is with immunomodulatory therapy, psychiatric symptoms often require adjuvant management.

• Resistance to traditional psychotropic agents, increased risk of EPSE & concern for lowering seizure threshold in patients already at risk of seizure, limits the use of psychotropics

• Autonomic disturbance including cardiac arrhythmias & reduced level of consciousness also increase the risk of drug-related side-effects. Symptoms of neurologic deterioration from progression of disease are similar to those of NMS, often prompting anti-psychotic withdrawal.
Aim

- To explore the use of ECT in NMDA encephalitis with a systematic literature review to ascertain whether it was safe & improved psychiatric outcomes.
- The role of ECT in treatment of neuropsychiatric symptoms & its effect on seizure threshold is discussed.
- Additionally we consider the ECT anaesthetic aspects, especially in association with autonomic instability.
Methods

• A systematic search of PubMed, Embase and PsycInfo databases from inception to June 2018 was completed using terms: NMDA, NMDAR, NMDARE, N-methyl-D-aspartate encephalitis, ECT and electroconvulsive therapy.
• All articles types that had data for individual cases were included.
• Search & screening was independently conducted by two authors at title, abstract & then full text level.
• References of selected articles were cross-checked to identify other potentially eligible studies.
Methods: Inclusion and exclusion

- Cases were included if they received treatment with ECT for anti-NMDA receptor encephalitis, & were diagnosed by positive serum or CSF IgG antibody.
- Cases with suspected but unconfirmed anti-NMDA receptor encephalitis, or those receiving ECT for other indications were excluded.
Methods: Data

- The pre-specified variables collected included: demographics, past medical & psychiatric history, initial & subsequent clinical presentation of encephalitis, investigations, psychotropic & other treatments, ECT timing and prescription, noted ECT side effects or other ECT considerations.
- Missing data was noted.
- Recognised anti-NMDA receptor encephalitis symptom clusters: psychiatric, cognitive, movement, seizures & autonomic, were used to classify initial presentation & course of illness. Descriptive statistics were employed for analysis of the data.
Results: Demographics

• There have been 781 published cases of NMDA encephalitis between 2007 – June 2018, of which 30 have used ECT.
• There were 22 females & 8 males.
• The mean age was 27.7 years (range 9-71 years) (SD 15.2).
• The youngest case was 9 years & there were 10 cases under the age of 18 years.
Results: Malignancy

Encephalitis associated with ovarian teratoma accounted for 4 cases, with no other malignancy noted in the remaining cases.
Results: Presenting feature

- The most common presenting feature of anti-NMDA receptor encephalitis in these cases was behavioural disturbance, 70% then psychosis, 36.7%. A single case presented with a seizure.
Results: Neurological abnormalities

- 67% of cases developed neurologic abnormalities, most commonly limb dystonia, orofacial dyskinesia, choreoathetosis & rigidity.
Results: Autonomic disturbance

- 56% developed autonomic disturbance - including tachycardia, hyperthermia and respiratory failure
- 53% had seizures
Results:

• Cognitive deficits during the active phase of illness was reported in 43.3%.
• 13.3% of cases had isolated psychiatric symptoms without other abnormalities.
• MRI brain was abnormal in 20% cases, reporting ischaemic foci 10%, T2 FLAIR hyperintensity 6.7% & one case of an incidental temporal lobe cyst with no oedema or mass effect. There were no identified contraindications to ECT on neuroimaging.
Results: EEG

- EEG on presentation was abnormal in 46.7%, documented as diffuse slow waves, extreme delta brush & one case demonstrating epileptiform features.
Results: Treatments

- Anti-psychotic medications were used in **83.3% of cases**, with 56.7% cases requiring multiple anti-psychotics.
- **Suspected NMS or severe EPSE** resulted in the cessation of anti-psychotics in 46.7% cases. A trial of benzodiazepines for catatonia was documented in 63.3% cases.
- ECT proceeded **without complication in 86.7%** of cases, with four cases prematurely ceasing ECT with further encephalitic deterioration. There were no anaesthetic complications.
- ECT was **commenced prior to the diagnosis** of anti-NMDA receptor encephalitis in 70%. The average number of sessions of ECT was 10, although this was not documented in 9 cases. Overall, the ECT dosage, placement and treatment course was poorly documented.
Results: Effect of ECT

• 76.7% of cases provided information on effectiveness of ECT.
• 65.2% noted improvement of psychiatric symptoms, and in 30% of the cases the improvement was seen prior to immunotherapy.
• In 13% cases it was documented that there was complete resolution of anti-NMDA receptor encephalitis symptoms with ECT, without any immunotherapy & after treatment resistance had been noted with psychotropics.
• In the 20% cases which improved with ECT & immunotherapy, it was documented that ECT was given due to insufficient response to immunotherapy alone.
• Interestingly, in 6.7% of cases, cognitive deficits were noted to resolve following ECT, & in 10% of cases there was also improvement of movement disorders, such as dyskinesia and rigidity.
Results: Recovery

- Complete recovery from anti-NMDA receptor encephalitis was documented in 60% cases, partial recovery in 33.3% cases, & not documented or lost to follow up in 6.7% cases.
- Of note, the 13.3% cases in which ECT was prematurely ceased made full recoveries following immunotherapy.
- In the 13.3% cases in which ECT was felt to be ineffective, 6.7% had complete recovery with immunotherapy, & in 6.7% there was no documentation.
- When recovery was partial this was due to ongoing cognitive deficits & in 16.7% of these cases the cognitive deficits were only documented after treatment.
- Recurrence of anti-NMDA receptor encephalitis was seen in 1 case, treated successfully with further immunotherapy.
Results: Safety

• In 26/30 cases (86.7%) there were no safety concerns.
• ECT was ceased prematurely in 4 cases. In 2 cases ECT was ceased after 1 session due to development of seizures. In the other 2 cases, ECT was ceased after 2 sessions due to concerns for neurological deterioration with limb dystonia and oro-facial dyskinesia reported.
• There were no documented complications from anaesthesia, with no requirement for reintubation or additional blood pressure/cardiac rhythm support.
Discussion
Possible beneficial anti-convulsant effect

• ECT has a known anti-convulsant effect & has been shown in animal models to prevent kindling, which may provide additional benefits to cases of anti-NMDA receptor encephalitis, known to progress to seizures in around 70%.
• Case series of epileptic psychiatric patients undergoing ECT, have shown it to be a safe & effective treatment.
• It is possible, that in the cases in which ECT was ceased due to seizure development, or other neurological symptoms, this was more reflective of the natural progression of anti-NMDA receptor encephalitis rather than a true side effect of ECT.
Discussion

• The primary treatment for anti-NMDA receptor encephalitis is immunomodulatory therapy, however, ECT appears to be a safe, effective adjuvant treatment for catatonia in this disorder.
• In most cases where ECT was used, symptoms had been refractory to other treatment, such as anti-psychotics or benzodiazepam challenge, or had required premature cessation of these medications due to side effects.
• Additionally, ECT proceeded safely in the majority, even in the context of neurological symptoms, seizures, autonomic disturbance, EEG and MRI changes.
Catatonia: ECT

- ECT has a high success rate of treating all types of catatonia.
- In addition to the effect of ECT in psychiatric disorders, it has also been effectively used in NMS, status epilepticus, & for dyskinesias & other motor symptoms in disorders such as Parkinson’s disease; potentially accounting for some of the beneficial motor effects seen in these cases.
- Conversely, ECT may just be temporarily attenuating the catatonic and motor symptoms, whilst effect of the immunomodulatory treatments or the natural progression of the disorder occurs.
- First line immunotherapy or tumour removal achieves symptom improvement for around 50% of anti-NMDA receptor encephalitis patients over 4 weeks, but for some, improvement may come up to 24 months later, even with second line immunotherapy. During that time there are risks of long term immobility, deconditioning & hospital acquired infections.
Anaesthetic considerations

- The anaesthetic considerations highlighted in the anti-NMDA receptor encephalitis literature were not raised in any of these cases, perhaps reflecting the brief anaesthetic required for ECT.
- Anaesthetics that act at the NMDA receptor, such as nitrous oxide and ketamine, may behave unpredictably in anti-NMDA receptor encephalitis. Ketamine was not used in any of these cases, but interest in gaining for its adjunct ECT anaesthetic use with a potential anti-depressant and neuroprotective cognitive effect, as well as, sparing some of the seizure shortening effect of Propofol.
- Propofol, has been used without concern in anti-NMDA receptor encephalitis.
- A non-depolarising muscle relaxant may be a safer alternative to succinylcholine, in the setting of potential hyperkalaemia with catatonic rigidity or longstanding immobility.
Consideration of autonomic disturbance

• Autonomic disturbance with alterations of temperature, heart rate and blood pressure, as well as respiratory depression, arrhythmias & asystole have been described in anti-NMDA receptor encephalitis.

• Tachycardia & fever occurred in over half of these cases without disruption to the ECT course, however, more severe autonomic disturbances such as central hypoventilation may pose greater concern, especially as prolonged airway protection with intubation does not routinely occur with ECT administration. ECT electrical stimulation, can result in a brief parasympathetic mediated bradycardia, hypotension & asystole, followed by a more prominent sympathetic response with hypertension and tachycardia. Awareness, assessment and availability of support is recommended.
Cognitive effects

• The cognitive effects of ECT in anti-NMDA receptor encephalitis are unclear, with both the resolution & onset of such deficits reported in these cases.

• Cognitive deficits, as an initial symptom as well as in both the active & recovery phases of anti-NMDA receptor encephalitis is common, thought to be due to impact on mesial-temporal structures.

• Early treatment & reduction of the active phase of illness, may result in improved cognitive outcomes, of which ECT may assist.

• Yet, ECT itself is associated with cognitive concerns. It is thought that the cognitive side effects of ECT are limited to within the first few days post treatment, with resolution beyond baseline seen after that in domains such as working memory, processing speeds, anterograde memory and executive functioning.

• Conflicting results may also be related to the inconsistent or non-specific documentation of cognition in these cases.
Limitations

• As the data was collected from case reports, the results are subject to selection, reporting & publication bias.
• There was limited documentation of ECT frequency, dose, electrode positioning, seizure quality & duration, preventing further analysis for ECT optimisation.
• The cases identified represent a small fraction of published anti-NMDA receptor encephalitis cases & cannot be generalised to those with non-psychiatric symptoms.
• It is interesting that most cases receiving ECT first presented with psychiatric features, possibly influencing the direction of care & the decision to trial ECT.
Summary

• ECT should be considered when patients are suffering from severe life psychiatric symptoms and/or catatonia.

• Further research is needed to define these parameters & confirm safety in a prospectively recruited cohort.
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