The Brain on Fire: A Case Study on Anti-NMDA Receptor Encephalitis

Grissel B Crasto [1].

[1]Toronto Western Hospital, Ontario

Abstract

Anti-NMDA receptor encephalitis is a rare disease that occurs when antibodies produced by the body's own immune system attack the N-methyl-d-aspartate (NMDA) receptors in the brain (Dalmau, 2016). For a relatively rare condition, one academic hospital in an urban centre noted four cases of anti-NMDA receptor encephalitis in one single year. Patients develop a multistage condition that progresses from psychosis, memory deficits, seizures, respiratory difficulties, abnormal catatonic movements and language disintegration into a state of unresponsiveness (Dalmau, Lancaster, Hernandez, Rosenfeld and Gordon, 2011).

This case study will focus on the pathologies and medical journeys of three female patients diagnosed with anti-N-NMDA receptor encephalitis at this hospital. This paper will discuss the presentations of each of the cases and the individualized nursing care plans developed to address the needs of this patient population. More specifically, it will highlight the importance of ensuring patient and staff safety in the development of these care plans. The need for implementing ongoing evaluations of these nursing care plans to address the developing needs of patients as they proceed through the diverse and complex phases of the condition will also be discussed.

Key Words

Anti-NMDA receptor encephalitis, autoimmune encephalitis, encephalitis, N-methyl-d-aspartate receptors

Introduction

Literature Review

In 2005, Dr. Josep Dalmau described a condition in four young women with ovarian teratomas and precipitating antibodies generated against antigens highly expressed in the hippocampus called N-methyl-d-aspartate (NMDA) receptors (Dalmau et al., 2011). NMDA receptors are concentrated in the hippocampus and play a vital role in synaptic adaptation processes that affect learning, memory, personality, movement and autonomic regulation (Newcomer, Farber & Olney, 2000). Antibodies are formed in response to antigens presented by a teratoma often found in the reproductive organs such as the ovaries or gonads and in some cases the antibodies formed are in response to neoplastic related antigens (Dalmau, 2016). These antibodies cross the blood brain barrier (BBB) and bind with NMDA receptors disrupting their synaptic functionalities and causing neurobehavioural pathology (Ding, Jian, Stary, Yi and Xiaoaxing, 2015). The down regulation of NMDA receptor activity in the hippocampus results in changes in synaptic plasticity affecting learning and memory (Day, High, Cot, & Tang-Wai, 2011).

Due to the pathology, patients may develop psychiatric symptoms, seizures, memory deficits and abnormal movements (Ding, et al., 2015). Focal neurological signs of the condition include decreased level of consciousness, weakness in limbs, seizures, altered behavioural patterns, memory loss and confusion (Dalmau et al., 2007). Patients present with psychiatric symptoms such as changes in personality, irritability or behavioural changes such as violence, agitation and paranoid thoughts. These symptoms are often misdiagnosed as their clinical presentation is consistent with psychosis and schizophrenia (Dalmau et al., 2007). The disruption of NMDA receptor activity also leads to disturbances in respiratory drive that cause hypoventilation (requiring ventilatory support) and impedes the body's autonomic functions

Questions or comments about this article should be directed to Grissel Crasto
Email address: crastogrissel@gmail.com

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that cause bradyarrhythmias (Dalmau et al., 2016). Moreover, patients are then admitted to psychiatric facilities instead of acute care facilities, which prolongs timely diagnosis and intervention (Dalmau et al., 2007). Alternatively, when patients are admitted to acute care facilities, the condition is often also mistaken for viral infections (Day et al., 2011).

Studies have linked early intervention and treatment with complete recovery. However, delay in treatment could result in death caused by neuronal degeneration, respiratory and/or cardiac failure (Dalmau, 2016). The risk of relapse has been noted in 20 to 25 percent of patients without teratomas, but this risk increases in patients if the teratomas have not been resected and treated appropriately (Ding et al., 2015). This further makes the case for anti-NMDAR encephalitis to be considered as a differential diagnosis when patients present with autonomic dysregulation, seizures and psychiatric features (Day et al., 2011).

Objective

The purpose of this case study is to raise awareness about this condition. It aims to encourage nurses, and other clinicians to consider it as a differential diagnosis in patients presenting with signs of fever, psychiatric symptoms, seizures, memory deficits, abnormal movements and autonomic dysfunction.

Epidemiology

The first anti-NMDAR encephalitis case was reported in 2005, but it was only characterized as a condition by Dr. Josef Dalmau in 2007 (Ding et al., 2015). The exact incidence of the condition is still not known (Kelly & Sexton, 2016). Anti-NMDAR encephalitis has been known as the most common cause of autoimmune encephalitis after acute demyelinating encephalomyelitis (Dalmau, 2016). This condition has been noted in children and adults of all ages (Dalmau et al., 2011). Approximately 60 percent of diagnosed cases are associated with tumours, but there are many documented cases with no detectable tumour. It tends to occur in both males and females, however 80 percent of the diagnosed cases as yet have been women (Dalmau, 2016). The condition has recently gained more attention in popular media. Susanah Cahalan, a journalist who worked for the New York Post shared a powerful narrative of her personal experiences with the condition in the book, 'The Brain on Fire'. For a relatively rare condition, one academic hospital in an urban centre treated four cases in a single year.

Clinical Presentation

A notable clinical manifestation of anti-NMDA receptor encephalitis involves a triad of specific features that present as epilepsy, dyskinesia and psychiatric symptoms (Omura et al., 2015). A list of general clinical features such as focal neurological signs, psychiatric signs and autonomic instability noted in various documented cases to date are listed in the Table 1.

Diagnostics

An analysis of serum and cerebrospinal fluid (CSF) via lumbar puncture (LP) is conducted to detect the presence of specific NMDA antibodies (Dalmau, 2016). In addition, brain imaging via computer tomography (CT) is used to detect changes in the brain and magnetic resonance imaging (MRI) is used to detect any underlying teratomas, particularly in the ovaries, gonads and mediastinal regions (Dalmau, 2016). Sometimes the tumours are undetectable and in these cases, a positron emission tomography (PET) scan may also be done (Kelly & Sexton, 2016). Furthermore, an electroencephalogram (EEG) may reveal abnormal and/or focal slowing with epileptiform discharges (Kelly & Sexton, 2016).

Table 1. Clinical features noted in patients with Anti-NMDAR receptor encephalitis

Focal neurological signs	Weakness in limbs, seizures, altered behaviour, memory loss, confusion
Psychiatric signs	Auditory, visual and olfactory hallucinations; irritability, agitation, aggression and violent behaviour; catatonia
Autonomic instability	Fever, tachycardia/bradycardia, hypotension/hypertension, hypoventilation

Treatments

In patients with primary tumours, the first course of treatment involves tumour resection (Halbert, 2016). As these tumours have predominantly been noted in the ovaries of female patients, a laparascopic oophorectomy can be performed (Dalmau et al., 2007). Patients are treated with first-line immunotherapy treatment. This includes corticosteroid therapy agents such as methylprednisolone, dexamethasone and prednisolone to reduce inflammation in the brain. Concurrent treatment with H2 receptor antagonists such as ranitidine or pantoprazole are given to prevent steroid induced mucosal damage (Omura et al., 2015). In addition, immunotherapies like intravenous immunoglobulin (IVIg) are administered to decrease inflammation of the meninges and inhibit the binding of anti-NMDA antibodies. Also, plasma exchange may be used for treatment by

Table 2. **Clinical presentations, treatments and outcome of cases seen at our hospital**

Case	Symptoms	Treatment	Adjunct therapies	Complications	Outcomes
F, 25, A	Aphasia, posturing (rigid), myoclonus jerks, tonic-clonic seizures, opsoclonus, decreased level of consciousness, respiratory difficulties, loss of tone, agitation, aggression	Bilateral Oopherectomy	ECT, Methylprednisolone, IVIG, Rituximab, Tetrabenzene, Quetiapine, Haloperidol, Olanzapine, Ketamine and Cyclophosphamide	Intubation, ventilator associated pneumonia, bacteremia, status epilepticus, febrile neutropenia	Complex care rehab, discharged home
F, 22, B	Confusion, hallucinations, global aphasia, agnosia, prosopagnosia, memory deficits, posturing, myoclonus and seizures Behavioural issues like cursing, spitting, yelling, agitation and aggression	Bilateral Oopherectomy	AEDs, Acyclovir, IVIG, plasmapheresis, methylprednisolone	Manic symptoms, psychosis (Psychiatry consulted for unresolved mania)	Repatriation, cognitive rehab, discharged home
F, 30, C	Brocca's aphasia progressed to global aphasia, parasthesia in arms, generalized seizures, hallucinations, sensitivity to light and noise, agnosia, prosopagnosia, falling spells and wandering	Right Oopherectomy RRR	Methylprednisolone, IVIG	UTI, allergic reaction to methylprednisolone (Psychiatry consulted for unresolved catatonia)	Cognitive rehab, discharged home

removing anti-NMDA antibodies from the blood (Dalmau et al., 2007). Second-line immunotherapies such as rituximab or cyclophosphamide, or both are used for patient showing little or no response to first-line immunotherapies (Dalmau, 2016).

Case Studies

Our first patient in 2016, whom we will refer to as Anna, was a 25-year-old, university student who presented to a community hospital with agitation, aggression, myoclonus jerks, generalized tonic clonic seizures, opsoclonus and tremors. Due to her psychiatric symptoms, she was initially misdiagnosed and treated with antipsychotic medications. She also received six sessions of electroconvulsive therapy. However, after noting a fever, rigidity and decreased level of consciousness, a lumbar puncture was performed. Anna tested positive for anti-NMDA receptor encephalitis. Although her MRI showed no signs of a teratoma, she was still treated with methylprednisolone and IVIg. After no improvements were noted, she was transferred to our Intensive Care Unit (ICU). She spent the next nine months in the ICU where she received plasma exchange and rituximab. She was further treated with tetrabenzine, quetiapine, haloperidol, olanzapine and ketamine to suppress the myoclonus jerks, yet no improvement was noted. Upon a repeat MRI, a tiny right cystic teratoma was noted on her ovary. Due to the severity of her symptoms and to prevent relapse, Anna received a bilateral oophorectomy and was subsequently treated for surgical menopause.

Anna went on to develop several complications in the ICU including bacteremia, ventilator associated pneumonia, status epilepticus and febrile neutropenia. Due to her slow recovery and following further consultation with Dr. Josef Dalmau, she was started on a monthly treatment of cyclophosphamide. After nine months, she was finally transferred to the inpatient unit where she presented with the symptoms outlined in Table 2. Her opsoclonus myoclonus and seizures were uncontrollable and putting her at high risk for falls.

We will refer to the next patient as Belle. She was a 22-year old female, who initially developed changes in her personality and started neglecting her personal hygiene following a vacation in Cuba. Belle was initially misdiagnosed with a psychiatric illness, started on anti-psychotic medications in a community hospital and discharged home. She was found unresponsive at home and re-admitted the following day. She also presented with posturing, rigidity and severe myclonus. Belle was treated with anti-epileptic drugs and Acyclovir for suspected viral encephalitis. Her MRI was normal, but her cerebrospinal fluid (CSF) tested positive for Anti-NMDA receptor antibodies at the community hospital. Upon confirmation of the diagnosis, she was transferred to the ICU at our centre.

Belle's symptoms were similar to Anna's symptoms. They both had hallucinations, agnosia and prosopaganosia as mentioned in Table 2. Furthermore, Belle presented with severe psychosis. She was cursing, spitting, yelling, was often whispering, agitated and aggressive. Belle was treated with IVIG, plasmapheresis and steroid therapy, but continued to have seizures. She was treated with multiple anti-epileptic medications. Her MRI showed no evidence of a teratoma. Despite this, the physicians chose a bilateral oophorectomy as she was deteriorating quickly. Her symptoms improved drastically after surgery. The pathology of her ovaries later revealed a microscopic teratoma. She was started on hormone therapy for surgically induced menopause and transferred to our inpatient unit. Despite improvements in her symptoms, her manic symptoms had not yet improved. A plan was needed to address Belle's manic symptoms, behavioural issues, her safety and the safety of staff caring for her during the agitated periods.

Our last patient (whom we will call Catherine), was a 30- year old female whose symptoms began with facial twitching and paresthesia in her right arm. She reported having some word finding difficulty for a week. Later in the week, she had a tonic-clonic seizure and fell down at a baseball game. Post-seizure, Catherine was brought to our emergency department for her progressive aphasia and a new onset of focal seizures. Her brain MRI and CT were unremarkable. An EEG showed diffused slowing, but no abnormalities. However, Catherine continued to present with global aphasia, visual hallucination, agnosia, falling spells and a sensitivity to light and noise (Table 2). Unlike Anna and Belle, she did not exhibit agitation nor aggression.

A pelvic MRI revealed a 5cm ovarian teratoma and an LP further confirmed the presence of anti-NMDAR antibodies in her CSF. She was started on IVIG treatments and her

teratoma was resected within eight days of her admission. She was also started on IV steroid therapy, but developed a reaction to it. As a result, the steroids were discontinued.

Nursing Implications

Acute Confusion Management

Each of these patients presented with unique and unpredictable symptoms making their medical management incredibly complex. Matata et al. (2015) suggests it is important for nurses to ensure a thorough Mini-mental status exam and Glasgow Coma Scale (GCS) assessment is performed to establish a patient's baseline on admission. Thereafter, a Confusion Assessment Method (CAM) and GCS must be performed regularly every shift in coordination with the physician's order. These tests enable nurses to detect minute changes in the patient's physiological and psychological status, and enhance communication to the team for psychiatric management. Matata et al. (2015) suggest that patients with this condition often develop paranoia. Thus, patients may benefit from nurses clustering their interventions to minimize stress and decrease stimulation (Matata et al., 2015). In addition, Matata et al. (2015) also suggest that the concerns of family or relatives at the bedside be taken seriously as they could be an indicator of the patient developing subtle psychiatric features. Nurses can play a crucial role in advocating for referrals to psychology, neuropsychology and mental health services within the interdisciplinary team.

Seizure Management

According to Dalmau et al., (2007), seizures are a characteristic symptom of the condition. Focal seizures, generalized seizures, status epilepticus and non-convulsive status epilepticus have all been noted in patients with Anti -NMDAR encephalitis (Dalmau, 2016). Nurses should monitor the patients closely for changes in behaviour and confusion as they could be signs of seizures. It is also important to prepare the bedside with safety equipment such as airway management equipment and intravenous (IV) access to allow for quick and effective seizure management in order to prevent brain injury.

Guven, Aydin & Kaykis (2017) define status epilepticus as a critical condition in which a seizure lasts for more than five minutes or when two or more seizures occur without any improvement. Brain injury can ensue as early as the five minutes into sustained seizure activity (Ramazan, et al., 2017). As a result, it is imperative to prepare for the administration of medications like IV lorazepam, phenytoin, midazolam and diazepam to manage status epilepticus effectively (Matata et al, 2015).

Non-convulsive status epilepticus (NCSE) in patients with an altered mental status have also been noted in this population (Day et al., 2011). Hassan (2016) describes NCSE as a prolonged seizure without perceptible motor signs but with an altered mental status and continuous epileptiform EEG changes. NCSE should be monitored closely for changes and communicate updates to the team as they may need continuous EEG monitoring and might need to be treated with anti-epileptic medications.

Memory Loss

Long term cognitive effects such as memory loss, disinhibition and impulsiveness, impairments in executive function such as inattention, poor organization and planning difficulties have been noted in this population (Bach, 2014). As a result, patients may require total assistance with activities of daily living (ADL). Occupational therapy and Physiotherapy may be required to help manage and to develop a plan care around the patient's general physical deconditioning (Tham, 2012).

All three of the previously discussed cases developed agnosia (inability to process sensation and recognize objects), prosopagnosia (inability to recognize faces), receptive aphasia (inability to comprehend language) and expressive aphasia (inability to speak) in some capacity (Dalmau et al., 2007). In addition, the patients also exhibited dysphagia and communication deficits, requiring a Speech Language Pathologist (SLP) consult.

Patient Safety, Staff Safety and Transitional Care

All our patients' families were quite involved in their care and tried to stay at the bedside as much as possible. However, when the families were unable to do so, a plan was developed for every single patient to ensure that their unique medical and psychosocial needs were being met, especially in regards to patient safety. The nurse to patient ratios on the inpatient unit is one to five versus one on one in the ICU. Their transitional needs

became more apparent during their transition from ICU to the inpatient unit. Families may have difficulty adjusting to the fact that the care provided on the inpatient unit is no longer on a one-on-one basis.

Families will require additional emotional support. Organizing family meetings can be helpful in communicating ongoing updates and establishing the goals of care. Nurses play a crucial role in initiating the discharge planning process from the point of admission and advocating for patients to receive all the appropriate referrals and services prior to discharge. Nursing representation at family meetings is also critical to help ensure families understand the plan and goals of care.

Due to the possibility of tonic-clonic seizures, posturing and myoclonus jerks, patients with anti-NMDAR are at high risk of falls. Strategies such as bed alarms, placing falls mats on the floor, ensuring the patient's belongings were within reach, establishing a toileting routine, providing non-slip slippers, placing the bed to the wall and de-cluttering the bedside space were quite useful in preventing falls in these patients.

Some patients with this condition may become quite violent and aggressive during the psychosis stage. It is recommended that a behavioural safety alert and plan be implemented to ensure the safety of the patient, family members and all staff in the interdisciplinary team. All possible options must be explored before the use of physical restraints such as soft mitts, restraint jackets and wrist restraints. It is recommended that chemical and physical restraints be used with caution to prevent patients from harming themselves, their families and staff. In addition to medical and safety concerns, another downside to the use of restraints is the distress it may cause to both patients and their family members. Nurses should provide ongoing emotional support to distressed family members as a

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part of the discussion about the goals of care for such patients. Other alternatives may be explored and agreed upon in discussion with family members at family meetings. For example, constant observers or "sitters" were organized for patients whose family members were distressed by the use of restraints for our patients.

Although medicine is more informed about the condition today than ever before, patients and families may struggle to cope with the rarity of the condition, the lack of information about the condition and the devastating effects of a oophorectomy or hysterectomy, early menopause and possible life altering changes. The families of all three patients were provided ongoing emotional support and offered spiritual care services or referred to hospital chaplains. They were also referred to support groups such as the Anti-NMDA Receptor Encephalitis Foundation and social services when appropriate.

Patient Outcomes

Anna was transferred to a Complex Care Rehabilitation facility and moved back home with her family. Although, Anna did not return completely back to her baseline, she is healthy again and doing very well. Her family says that her cognition has improved, and that she is talking and walking again. Her family also mentioned she is attending day programs three times a week and spending a lot of time engaged in activities with family and friends.

A Psychiatry consult was arranged for Belle and she was started on anti-psychotic medications to manage her agitation and violent behaviour. Upon successful medical and psychological management, Belle was repatriated to a community hospital in her hometown for further monitoring. She received cognitive rehab for two months and she is still receiving treatment on an outpatient basis. She is currently working through a program offered by the March of Dimes of Canada. The community based rehabilitation program helps people with disabilities transition back into the work force. As per family, she has almost returned back to her baseline and hopes to attend college next year.

Following her improvement, Catherine was discharged to a cognitive rehabilitation centre close to her family home. She has almost completely recovered, has returned to work at her previous position. She continues to be followed by Neuropsychiatry at our hospital.

Discussion

Prior to 2005, undiagnosed and untreated patients with this condition often developed complications such as infections, cognitive and motor dysfunction, life long impairments and even death (Dalmau et al., 2007). In a multi-institutional observation study Titulaer et al. (2013) reported that out of 577 patients, 495 became bedridden and 440 were admitted to the ICU at some point, 394 went on to reach good outcomes and 30 patients ended up dying. The patients in this case study presented with both neurological and psychiatric features similar to those noted in literature. However, thanks to the advances made by Dr. Josef Dalmau, in comparison to cases prior to 2005, the patients in this case study faired relatively well with two going back to work and one returning home to live with her family. The value of early diagnosis and treatment is colossal to the successful recovery of patients suffering from anti-NMDAR encephalitis.

In summary, the triad noted often in this patient population is seizures, psychosis and dyskinesia (Dalmau, 2016). Based on their observational study, Titulaer et al. (2013) suggest that early diagnosis and timely intervention is predictive of improved outcomes in this patient population. Nurses, physicians and allied health professionals especially in community health, emergency and neurology departments, family medicine and psychiatric facilities play an integral role in recognizing symptoms earlier on and facilitating or delivering timely medical intervention to these patients. Nurses in particular play a crucial role in supporting patients and their families through this rare and distressing neurological condition. Nursing implications include regularly communicating ongoing neurological developments to the team, acute confusion management, seizure management, respiratory and cardiac monitoring, making appropriate referrals, patient advocacy, providing emotional support, coordinating additional support services, educating patients and families, ensuring patient and staff safety and discharge planning.

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References

Bach, L. J., (2014). Long Term Rehabilitation Management and outcome of anti-NMDA receptor encephalitis: Case Reports. Neurorehabilitation 35: 863-875.

Dalmau, J., (2016). NMDA receptor encephalitis and other antibody-mediated disorders

of the synapse-The 2016 Cotzias Lecture. American Academy of Neurology, 87:2471-2482.

Dalmau, J., Lancaster, E., Matinez-Hernandez, E., Rosenfeld, M., Balice-Gordon, R., (2011). Clinical Experience and Laboratory Investigations in patients with Anti - NMDA receptor encephalitis. The Lancet – Neurology 10 (1): 63-74.

Dalmau, J., Tuzun, E., Wu, H., Masjuan, J., Rossi, J. E., Voloschin, A., Lynch, D. R., (2007). Paraneoplastic Anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Annals of Neurology, 61:25-36.

Day, G. S., High, S. M., Cot, B. & Tang-Wai, D., (2011). Anti-NMDA receptor Encephalitis: Case report and literature review of an under-recognized condition. Journal of General Internal Medicine, 26 (7): 811-816.

Day, G. S., Laiq, S., Tang-Wai, D. F. & Munhoz, D., (2014). Abnormal neurons in teratomas in NMDAR encephalitis. JAMA Neurology, 71 (6):717-724.

Ding, H., Jian, Z, Stary, C. M., Yi, W and Xiaoaxing, X., (2015). Molecualr Pathogenesis of Anti-NMDAR encephalitis. BioMed Research International, 1: 1-6.

Guven, R., Aydin, M. N. and Kaykisiz, E. K., (2017). An emergency medicine perspective for non-convulsive status epilepticus. Eurasian Journal of Emergency Medicine. 16: 83-89.

Halbert, R. K., (2016). Anti-N-methyl-D-aspartate receptor encpehalitis. Journal of Neuroscience Nursing, 48(5): 270-273.

Hasan, A., Q., (2016). Non Convulsive Status Epilepticus in Emergency Department: A diagnostic Challenge. Journal of Medical Science and Clinical Research, 4(8): 12305-12308.

Kelly, L. J., & Sexton, V. L., (2016). Anti NMDA encephalitis. The Neurodiagnostic Journal, 56:101-108.

Matata, C et al., (2015). Managing patients with encephalitis. Nursing Standard,30(11): 50-58.

Newcomer, J. W., Farber, N. B. & Olney, J. W., (2000). NMDA receptor function, memory, and brain aging. Dialogues in Clinical Neurosciences, 2(3): 219–232.

Omura, T., Sonoda, S., Nagata, K., Okita, T., Hoshiai, A., Sano, H., Shoichi, O., (2015). Acute Medicine & Surgery, 2: 56-59.

Titulaer, M. J., McCracken, L., Gabilondo, I., Armangue, T., Glaser, C., Lizuka, T., … Dalmau, J., (2013). Treatment and prgnostic factors for long-term outcome in patients with anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis: a cohort study. The Lancet – Neurology 12 (2): 157-165.

Tham SL, Kong KH (2012) A case of anti-NMDAR (N-methyl-D- aspartate receptor) encephalitis: a rehabilitation perspective. NeuroRehabilitation. 30 (2) 109-112.