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Editorial

Celebrating 50 years

Editorial

With only two years until the 13th Quadrennial Congress it is time for all of us to consider the great work that we are doing and start thinking about potential abstract submissions. Two years might seem a long way away, but it will come around quickly. I have recently had the absolute privilege to represent my workplace, Australia and the neuroscience nursing community at the European Stroke Organisation Conference in Milan. I was one of over 5600 participants enjoying a packed program, including the 1348 electronic posters. I wore my ANNA and WFNN badges and it was incredible to meet up with other nurses from around the world who recognised the WFNN badge.

Some of the nursing highlights to mention were the presentation topics including: long-term trends in care needs of stroke survivors, caregiver stress post stroke in a developing country, aphasia treatment sessions, pneumonia risk reduction through screening, community-based rehabilitation, preparedness assessments for caregivers, improving psychological well being post stroke and computer game-based therapy. The presentations and posters were exceptionally creative in their solutions to real problems within workplaces across so many different settings and countries that were all facing their own challenges be it economic, geographical, or socioeconomic. The presentations offered real solutions to problems and took holistic, interdisciplinary and often long-term approaches to improving outcomes for individuals and caregivers post a stroke event.

It was incredible and inspiring to see so many nurse led projects and they certainly have me thinking about the upcoming ANNA Annual Conference that will be held on 17-18th October 2019 at the Intercontinental Hotel in Wellington, New Zealand.

Linda

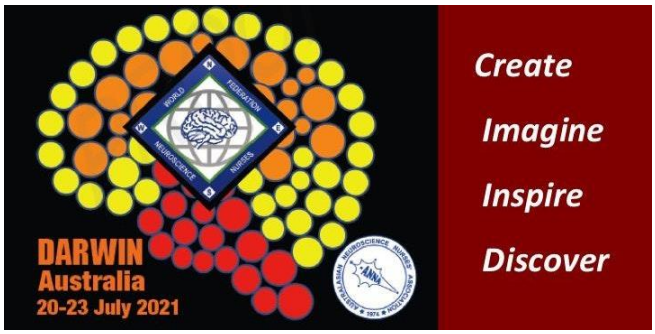
Linda Nichols
Editor

In 1969 the World Federation of Neuroscience Nursing (WFNN) was conceptualised by Agnes Marshall with the goal of connecting the neuroscience nursing community through the goals of education, support and development of associations. Over the last 50 years the WFNN has continued to grow, not only in numbers but also across speciality fields and most importantly across countries and regions.

Agnes legacy also includes being a cofounder of the American Association of Neuroscience Nurses (AANN) and subsequently elected President of AANN in 1969. She participated in the development of a certification program for neuroscience nurses, as well as being a founding member of the American Board of Neuroscience Nursing (ABNN), where she also served as President.

As we celebrate these 50 years we also celebrate the success of the Quadrennial Congresses from 1973 to the upcoming congress in 2021. Throughout this time neuroscience nurses have been networking, collaborating and sharing skills, expertise, research and friendship.

The last Congress held in Australia was in 2001 (Sydney) and 20 years later Australia will host the 13th Quadrennial Congress in Darwin from 20th-23rd of July 2021. This is an exciting time for us to all consider how we can create, imagine, inspire and discover.



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

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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

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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, discharge 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

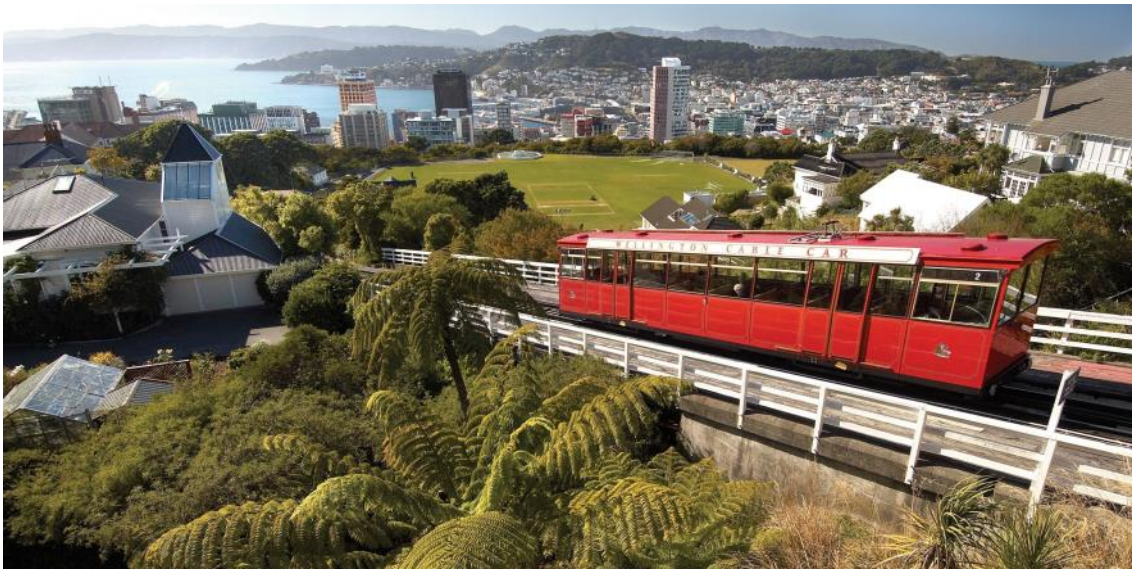
All our patients' families were quite involved in their care and tried to stay at the bedside as much as possible. However, when the families were unable to do so, a plan was developed for every single patient to ensure that their unique medical and psychosocial needs were being met, especially in regards 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



Save the Date!

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The 2019 ANNA National Conference will be an action-packed two days of professional development and networking at the Intercontinental Hotel in Wellington, New Zealand!

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We look forward to seeing you there!

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.

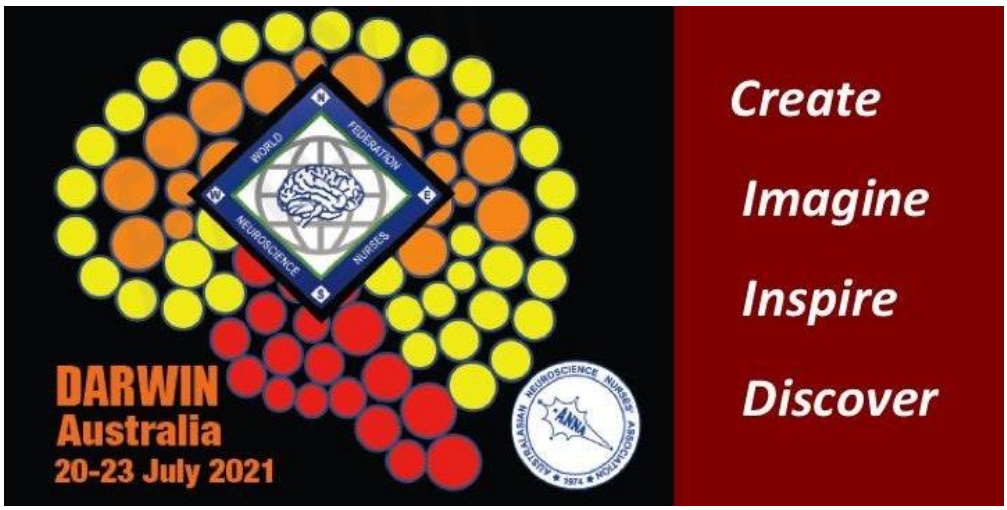
Matata, C et al., (2015). Managing patients with encephalitis. Nursing Standard,30(11): 50-58.

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.



Considering Causes for Hypoactive Delirium

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Abstract

Delirium is defined as a mental disorder characterized by an abnormal state of cognition and awareness. Delirium is associated with an annual cost of $350 billion between the United States and Europe. Approximately 80% of delirium cases are either not identified or misdiagnosed. Older adults have the highest incidence due to the consequences of aging. Hypoactive delirium or "quite delirium" is the most common delirium subtype experienced by older adults.

Hypoactive delirium, is difficult to recognize and has worse outcomes than other subtypes. If detected, symptoms of hypoactive delirium are frequently dismissed as depression or dementia. Therefore, nurses need heightened vigilance in assessment and identification of hypoactive delirium. This article seeks to assist nurses in identifying hypoactive delirium by outlining factors that increase an individual's potential for developing hypoactive delirium.

Key Words

Delirium, Hypoactive, Pathophysiology, Nursing Care, Subtype.

Introduction

Delirium was defined by the American Psychiatric Association as a mental disorder characterized by an abnormal state of cognition and awareness (American Psychiatric Association, 1987). Additional delirium features include disorientation, inattention, misperception and hallucinations (American Psychiatric Association, 1987). Delirium subtypes (hypoactive, hyperactive and mixed) were identified in 1983, by Lipowski (Lipowski, 1983). The hypoactive subtype is frequently called "pure lethargy" or "quiet delirium." See Table 1. It manifests itself as decreased psychomotor activity, lethargy, inattention, slow responses to questions, and looks similar to depression and sedation (Bui, Pham, Shirkey, & Swan, 2017; Bush et al., 2017; Han et al., 2009; Wan, Kasliwal, McKenzie, & Barrett, 2011). As a result, it is often overlooked without a standardized delirium assessment (Han et al., 2009; Robinson, Raeburn, Tran, Brenner, & Moss, 2011; Zhang et al., 2016).

Like all delirium subtypes, hypoactive delirium can occur in a variety of individuals and settings. However, hypoactive delirium receives the least attention and is more difficult to recognize (American Psychiatric Association, 2013; Bush et al., 2017). Individuals with hyperactive or mixed delirium are 50% more likely to be identified than those with the hypoactive subtype (Bush, Marchington et al. 2017). Bui et al. (2017) compared delirium presence to International Classifications of Diseases (ICD) coding finding that only 3% of individuals who were delirium positive had a diagnosis of delirium due to lack of recognition or misdiagnosis (Bui et al., 2017).

Delirium triples mortality risk, however, rates are considerably higher in the setting of hypoactive delirium (Bui et al., 2017). Further complicating hypoactive delirium, survivors frequently have greater risk for long term cognitive impairment (Bush et al., 2017; Lipowski, 1983; van den Boogaard, Schoonhoven, van der Hoeven, van Achterberg, & Pickkers, 2012). A study by Avelino-Silva (2018) found 38% of hospitalized patients will die within 12 months of hospitalization. Of the 38% who died, delirium occurred in 47% of hospital admissions (Avelina-Silva, 2018). When comparing delirium subtype, hypoactive delirium was associated with 33% of the

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Table 1. Delirium Subtypes

Delirium Subtype	Definition /Defining Characteristics
Delirium	An acute fluctuating disturbance in attention, cognition, and level of consciousness
Hyperactive	Agitation Aggressiveness. Fidgety or restless Speaks quickly and loudly Vigilant Readily distracted Verbal and physical agitation Effective communication is difficult Hallucinations and delusions
Hypoactive	Motor retardation, Apathy Slowing of speech, Appears to be sedated Lethargic and quiet. Unusually listless Appears depressed Lack of motivation Withdrawn Almost mute Extreme stupor
Mixed	Combination of hyperactive and hypoactive delirium

cases and a hazard ratio of 2.43 (95%-1.64-3.59). The high mortality rates are likely because only 12% of nurses can definitively identify its core features resulting in delayed or missed identification (Bui et al., 2017; Bush et al., 2017).

While the underlying etiology is not completely clear, proposed mechanisms include metabolic derangements, inflammation, and neurotransmitter imbalances (van den Boogaard, Schoonhoven, Evers, et al., 2012). It is likely a combination of the three mechanisms that explain the evolution of hypoactive delirium. For example, as individuals adapt to overwhelming physiological stressors, inflammation ensues and alterations in neurotransmitters (mainly dopamine and acetylcholine) lead to behavioral symptoms (Mulkey, Hardin, Olson, & Munro, 2018). Predisposing factors particularly associated with the hypoactive subtype include advanced age, prior cognitive impairment, and medications (especially sedatives). As many as 80% of older adults experience delirium during hospitalization (Mulkey, Hardin, et al., 2018). Of those experiencing delirium, the hypoactive subtype accounts for 65% (Inouye, Westendorp, & Saczynski, 2014; van Velthuijsen, Zwakhalen, Mulder, Verhey, & Kempen, 2017) When combined predisposing factors with risk factors such as higher severity of illness, organ failure, metabolic abnormalities, hypoxia and/or anoxia, hypoactive delirium evolves (Hosker & Ward, 2017). One study found causes associated with delirium were infections at 38%, surgery at 24%, 5% were associated with medication use and 3% were related to falls. The remaining 30% had no established direct cause (van Velthuijsen et al., 2017). Another study looking at the frequency of delirium in older adults with dementia found as many as 89% of individuals with dementia develop delirium in the hospital (van Velthuijsen et al., 2017). This article seeks to assist nurses in identifying hypoactive delirium by outlining factors that increase an individual's potential for developing hypoactive delirium.

Advanced Age

Because of normal physiological changes, older adults are more likely to develop hypoactive delirium OR 3.3 (1.9-5.9) (Peterson et al., 2006). The aging process leads to declines in functional reserve, especially for those over 70 years of age. As a result, risk for hypoactive delirium triples (Bilotta, Lauretta, Borozdina, Mizikov, & Rosa, 2013). For

example, an age associated reduction in acetylcholine reduces the brain's ability to respond to stress (Mulkey, Hardin, et al., 2018).

Older adults often have a reduction in pulmonary vital capacity as high as 40% (Lowery, Brubaker, Kuhlmann, & Kovacs, 2013). As physiologic stress increases, cerebral oxygen delivery is diminished; further reducing the brain's ability to compensate. Therefore, even mild hypoxia can lead to decreased cognitive function (Maldonado, 2008). A multivariate analysis revealed that individuals with the hypoactive and mixed subtypes of delirium survived for shorter periods compared to individuals without delirium (hazard ratio [HR] =1.65 [95% confidence interval (CI) = 1.05–2.59, p = .029] and HR = 2.30 [95% CI = 1.44–3.69, p = .001], respectively in a cohort of palliative care patients (Kim, Kim, Bae, Park, & Kim, 2015). Therefore, nurses should have a heightened suspicion for delirium in older adults with an acute or critical illness, especially in the presence of co-morbid condition.

Prior Cognitive Impairmen

Prior cognitive impairment, such as dementia, is a significant risk factor for hypoactive delirium (Avelino-Silva, Campora, Curiati, & Jacob-Filho, 2017; Davis et al., 2015; Peritogiannis, Bolosi, Lixouriotis, & Rizos, 2015). Susceptibility to acute insults increases with underlying cognitive or neurodegenerative pathology (Davis et al., 2015). Synaptic loss related to dementia is a strong correlate of cognitive decline and neuronal pathology occurring years before signs of impairment (Avelino-Silva et al., 2017). The progressive degeneration represents significant brain disconnectivity and quantifiable loss of "brain reserve," or ability to compensate (Avelino-Silva et al., 2017; Numan et al., 2017; Rowe et al., 2015).

Although synaptic disconnection is a major contributor to delirium, other aspects of dementia, such as activation of the immune system and cholinergic dysfunction, are also likely contributors (Avelino-Silva et al., 2017; Davis et al., 2015; Numan et al., 2017). These factors contribute to the overall brain function frailty and simply reveal the degenerating brain's inability to compensate during times of overwhelming acute stress, such as critical illness (Avelino-Silva et al., 2017; Davis et al., 2015). Therefore, while not the cause, delirium may unmask an underlying neurodegenerative process such as dementia. These underlying neurodegenerative processes in turn, increase the susceptibility to delirium. Because prior cognitive impairment increases the brain's vulnerability, nurses should closely monitor any patient admitted with a history of dementia, brain injury or other cerebral conditions.

Medications

Factors associated with medication related hypoactive delirium include the number of medications or polypharmacy (generally > 3), the drug's anticholinergic potential, and the use of psychoactive medications (Kruskal-Wallis test: 17.39, p<0.005) (Horacek, Krnacova, Prasko, & Latalova, 2016). The number of agents is associated with the pharmacokinetic and pharmacodynamic effects of combining agents (e.g., drug-drug interactions, metabolic inhibitions, and additive negative effects) (Mulkey, Hardin, et al., 2018). Therefore, nurses should suspect the development delirium in patients with more than three medications such as those with multiple co-morbidities or advanced age.

Medications with psychoactive activity (i.e., opiates, benzodiazepines and anticholinergics) contribute to as much as 75% of hypoactive delirium (Horacek et al., 2016; Numan et al., 2017). Sedative agents contribute through several mechanisms. Sedatives decrease the amount of acetylcholine causing an acetylcholine deficiency. This deficiency results in a disruption of the blood-brain barrier's (BBB) ability to act as a filter, meaning the ability to restrict what crosses over from central circulation into cerebral circulation is impaired, therefore, neuronal damage is enhanced. Anticholinergics are also associated with a subsequent increase in symptom severity (Maldonado, 2008). Even after adjusting for physical impairment and admission diagnosis, anticholinergic drugs can double the risk for hypoactive delirium in acutely ill older adults.

Among sedatives, GABAergic medications (i.e. lorazepam and propofol) are the most significant and frequent culprits causing hypoactive delirium. Propofol has a higher incidence because it significantly reduces the brain's information integration capacity (Bilotta et al., 2013). Additionally, lorazepam increases the daily risk for delirium transition (Maldonado, 2008). Meagher (2011) found 15/35 or 42% of transitions into the hypoactive subtype were preceded by increased benzodiazepine dosing. In turn, benzodiazepine antagonists have been shown to reverse coma and improve hypoactive delirium, particularly in hepatic encephalopathy. Delirium has been found to increase length of time requiring mechanical ventilation [OR 7.0 (4.7-10.5)] more frequently than sedative use alone [OR 2.9 (1.8-4.6)]. These alterations result in sensory overload and a disruption of

the circadian rhythm, thereby, interfering with physiologic sleep patterns (Numan et al., 2017). Therefore, polypharmacy, anticholinergics and/or use of psychoactive drugs are one of the primary risk factors that quadruple the risk for developing hypoactive delirium (Rowe et al., 2015). Nurses need to be aware of the increased risk for developing delirium in patients with receiving sedatives, psychoactives or any anticholinergic medications.

Critical Illness

Illness, trauma, and surgical procedures offer several triggering factors: anesthetic use, extensive tissue trauma, blood loss and anemia, blood transfusions, hypoxia, and initiating the inflammatory process (Horacek et al., 2016). van den Boogaard (2012) found hypoactive delirium increased ICU length of stay (LOS) from 1-5 days to 2-9 days and hospital LOS from 1-5 days to 8-32 days. The severity of the initial injury or underlying medical condition, mechanical ventilation and high Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) scores are significantly directly correlated with hypoactive delirium (Adamis, Meagher, Rooney, Mulligan, & McCarthy, 2017).

In a recent meta-analysis, mortality rates were significantly higher in individuals with reduced levels of consciousness admitted with respiratory conditions (38%). Respiratory conditions were found to increase the odds of developing delirium (OR 3.35 [2.59, 4.33] higher than cardiac at 5.4% (OR 10.00 [3.6, 27.76], endocrine at 2.5% (OR 25.6 [4.05, 161.73]) or gastrointestinal at 5.9% with odds ratios of 11.26 [4.34, 29.25] conditions (Todd et al., 2017). The more intense the insult, the more pronounced the response.

The combination of an intense insult such as an acute infection or trauma, and the associated systemic inflammatory response result in high levels of stress capable of altering BBB permeability. This leads to the initiation of a cerebral inflammatory response and release of cerebral cytokines (Kozak et al., 2017). As a result, there are shifts in extravascular fluid with potential to develop perivascular edema. With the formation of edema, there is a significant risk for diffuse microcirculatory impairment along with decreased perfusion and longer oxygen diffusion distances (Kozak et al., 2017).

Cerebral and systemic leukocyte activation (immune response) result in release of free oxygen radicals and enzymes exacerbating the systemic inflammatory response and further contributing to the evolution of hypoactive delirium (Bergeron, Dubois, Dumont, Dial, & Skrobik, 2001; Nguyen et al., 2014; van den Boogaard, Schoonhoven, Evers, et al., 2012). Therefore, delirium may represent a central nervous system manifestation of a systemic disease state that has crossed the BBB. Because critical illness increases physiologic stress on the brain, patients in critical care units are particularly vulnerable and should be routinely monitored for an appropriate standardized delirium screening tool (Mulkey, Roberson, Everhart, & Hardin, 2018).

Organ Failure and Metabolic Abnormalities

Abnormal laboratory values can significantly increase the risk of hypoactive delirium in all populations OR 3.4 (1.3-8.7) (Bilotta et al., 2013; Horacek et al., 2016; Inouye et al., 2014). Alterations in sodium (sodium <130 or >150 mEq/L) and potassium (<3.0 or >6.0 mEq/L) levels (Pearson's r=0.2189, P< 0.05), as well as other electrolyte, can lead to the mental status changes associated with delirium. While not clearly understood, sodium imbalances lead to cellular swelling, thereby impairing oxygen delivery (Maldonado, 2008). In the elderly, electrolyte abnormalities, especially hyponatremia, often caused by renal disease and chronic diuretic therapy should be promptly corrected (Bilotta et al., 2013). Patients with an increased risk electrolyte abnormalities such as those with renal impairment, diabetes, cirrhosis or the presence of electrolyte imbalances should be closely observed for signs and symptoms of delirium.

Dehydration, fluid deficits, prolonged fasting time (> 6 hours), and low serum albumin concentrations contribute because of hypoperfusion, both cerebral and renal (Horacek et al., 2016). This is thought to be due to increased drug and metabolite concentrations and decreased renal elimination of drugs, metabolites, and toxic by-products. Failure to correct hypoglycemia (<60 mg/dL), hyperglycemia (>300 mg/dL), and anemia (Hb <120g/L) are risk factors due to the effects on brain metabolism and oxygen transport. For example, Horace (2016) found low Hb levels (<120g/L) increased delirium duration by 11 hours. These alterations induce drug and hormone binding activity along with antioxidant and oxygen radical trapping and are correlated with cognitive impairment. Because of the associated impairment in cognitive performance these abnormalities are considered precipitating factors (Horacek et al., 2016).

Therefore, nurses should be suspicious for delirium in patients who have an increased risk for dehydration or anemia such as post-

operative patients and those with acute bleeding.

Hypoxia and Anoxia

Hypoxia and global mild ischemic illness injury often co-exist with critical illness, increasing oxidative failure. This correlates with a 17% increased risk for developing hypoactive as well as delirium progression (Bilotta et al., 2013; Maldonado, 2008; Stransky et al., 2011). Low hemoglobin, hematocrit, and pulse oximetry occur approximately 48 hours before the onset of oxidative stress with alterations being more severe in individuals experiencing hypoactive delirium (Maldonado, 2008; Stransky et al., 2011). Severe illness, combined with decreased oxygen supply and/or increased oxygen demand leads to decreased cerebral oxygen availability (Maldonado, 2008). Inadequate oxygenation leads to abnormal neurotransmitter function, ineffective elimination of neurotoxic by-products, and alterations in electrolytes (Numan et al., 2017).

Rapid depletion of energy stores from cerebral ischemia result in cell death. These changes then result in reconfiguration of neuronal networks. For example, sepsis causes an oxygen supply and demand imbalance due to lower hemoglobin level, cerebral blood flow, and cerebral oxygen delivery (Nedergaard, Jensen, Stylsvig, Lauridsen, & Toft, 2016). In critically ill delirious patients, reduced cerebral blood flow and the associated imbalances increase the chronic hypoxic injury. Patients admitted with an acute respiratory distress or failure and those with a history of respiratory conditions such as asthma and COPD are at increased risk.

Identification and Assessment

Using a standardized assessment tool for sedation and agitation can assist with identifying patients who may be developing hypoactive and hyperactive delirium symptoms (Mulkey, Roberson, et al., 2018). Likewise, use of these assessment screening tools can differentiate delirium subtypes in patients identified. The Richmond Agitation Sedation Scale (RASS) is a component of the Confusion Assessment Method- Intensive Care Unit (CAM-ICU). Scoring is based on the individual's activity with -5 being nonresponsive to +4 being agitated and combative. Individuals with a RASS of -2 to +4 are considered appropriate for delirium assessment with the CAM-ICU. If the CAM-ICU is positive for delirium, the RASS score can also be used to indicate a delirium subtype. Individuals with a lower score (0 to -3) are considered hypoactive while a higher score (+1 to +4) indicates hyperactive delirium (Michaud, Bullard, Harris, & Thomas, 2015; Peterson et al., 2006).

Nursing Implications

Table 2. Implications for Practice

Hypoactive delirium is difficult to detect
Understanding clinical features and risk factors is critical for detection
Standardized assessment tools appropriate for the population should be used
Frequent assessments are needed because delirium fluctuates
Prevention and intervention strategies should be implemented early
Regularly assess medication for delirium risk and response
Strongly consider continuation of home medications,
Promote adequate pain management and reduction of sedation to the minimum dose required
Early mobility, limiting restraint, adequate hydration and nutrition are key to prevention and treatment
Timing of care should promote periods of uninterrupted rest and sleep (i.e. giving up middle of the night bathing, timing of medication administration and routine lab/x-rays)
Establishing day and night routines will reduce risk and help resolve delirium

Nurses are the cornerstone to prevention and identification of hypoactive delirium and preventing the associated negative sequela. Because hypoactive delirium is more difficult to detect, nurses need to ensure they understand the clinical features and risk factors. For early accurate detection nurses should frequently assess individuals using an appropriate standardized tool. Maintaining consistency and accuracy of assessments has been identified as a significant challenge to obtaining ongoing accurate assessments. (See Table 2) Understanding factors that increase an individual's risk for developing delirium will assist with identification, and selection of prevention and intervention strategies specific to the individual. Because medications can have a significant impact on delirium risk, medications and patient response should be reviewed on an ongoing basis. Serious consideration should be directed toward continuation of home medications, adequate pain management and reducing sedation to the minimum dose required.

Early mobility, limiting use of restraints, adequate hydration, and limiting interruptions to maintaining adequate nutrition are key to prevention and treatment of delirium. Finally, timing of care is also extremely important. Promoting quiet time consistent with circadian rhythms (2-4 am & 2-4 pm), uninterrupted sleep, establishing day and night routines and timing of care (i.e. giving up middle of the night bathing, timing of medication administration and routine lab/x-rays) will reduce risk and help resolve delirium. To assist in remembering key components of nursing care vital to delirium management, the following acronym Q-U-I-E-T has been provided. (See Table 3)

Conclusion

Often unrecognized and underappreciated, hypoactive delirium or "quiet delirium" is more difficult to detect, therefore, frequently associated with delays in delirium treatment and increased mortality (up to 58%) (Todd et al., 2017). Advanced age and prior cognitive impairment are predisposing factors due to a reduced ability to compensate for neurochemical changes. Medications with anticholinergic or sedative effects and severe illness result in higher levels of stress. While there are many causes for hypoactive delirium, combining risk factors, as seen in critical illness, magnifies these risks. Understanding the risk factors will allow nurses to identify the presence of hypoactive delirium. Identification through ongoing assessment for delirium is of the utmost importance (Peritogiannis et al., 2015).

Reflective Questions

How is hypoactive delirium different from other delirium subtypes, and why is it important?

Of the individuals I care for, who is at greatest risk for developing hypoactive delirium?

What interventions might be appropriate for the prevention of hypoactive delirium?

Do I currently provide care that promotes the prevention of delirium?

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References

Adamis, D., Meagher, D., Rooney, S., Mulligan, O., & McCarthy, G. (2017). A comparison of outcomes according to different diagnostic systems for delirium (DSM-5, DSM-IV, CAM, and DRS-R98). International Psychogeriatrics, 1-6. doi:10.1017s1041610217001697

American Psychiatric Association. (1987). Diagnostic and Statistical Manual of Mental Disorders: DSM-III-R (3rd, rev. ed.). Washington, DC: American Psychiatric Association.

Table 3. Nursing Delirium Prevention Strategies

Q- Quick and Accurate Assessment with a validated tool

U- Understand Risk Factor

I- Initiate Discussion of Home Medications, Adequate Pain Control and Minimizing Sedation

E- Encourage Early Mobility, Nutrition, Hydration, and Restraint Release

T- Timing of Care to Promote Sleep

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: DSM-5 (Fifth ed.). Arlington, VA: American Psychiatric Association.

Avelino-Silva, T. J., Campora, F., Curiati, J. A., & Jacob-Filho, W. (2017). Association between delirium superimposed on dementia and mortality in hospitalized older adults: A prospective cohort study. PLoS Medicine, 14 (3), e1002264. doi:10.1371/journal.pmed.1002264

Bergeron, N., Dubois, M. J., Dumont, M., Dial, S., & Skrobik, Y. (2001). Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Medicine, 27(5), 859-864.

Bilotta, F., Lauretta, M. P., Borozdina, A., Mizikov, V. M., & Rosa, G. (2013). Postoperative delirium: Risk factors, diagnosis and perioperative care. Minerva Anestesiologica, 79(9), 1066-1076.

Bui, L. N., Pham, V. P., Shirkey, B. A., & Swan, J. T. (2017). Effect of delirium motoric subtypes on administrative documentation of delirium in the surgical intensive care unit. Journal of Clinical Monitoring and Computing, 31(3), 631-640. doi:10.1007/s10877-016-9873-1

Bush, S. H., Marchington, K. L., Agar, M., Davis, D. H., Sikora, L., & Tsang, T. W. (2017). Quality of clinical practice guidelines in delirium: a systematic appraisal. BMJ Open, 7(3), e013809. doi:10.1136/bmjopen-2016-013809

Davis, D. H., Skelly, D. T., Murray, C., Hennessy, E., Bowen, J., Norton, S., . . . Cunningham, C. (2015). Worsening cognitive impairment and neurodegenerative pathology progressively increase risk for delirium. American Journal of Geriatric Psychiatry, 23 (4), 403-415. doi:10.1016/j.jagp.2014.08.005

Han, J. H., Morandi, A., Ely, E. W., Callison, C., Zhou, C., Storrow, A. B., . . . Schnelle, J. (2009). Delirium in the nursing home patients seen in the emergency department. Journal of the American Geriatrics Society, 57(5), 889-894. doi:10.1111/j.1532-5415.2009.02219.x

Horacek, R., Krnacova, B., Prasko, J., & Latalova, K. (2016). Delirium as a complication of the surgical intensive care. Neuropsychiatric Disease and Treatment, 12, 2425-2434. doi:10.2147/NDT.S115800

Hosker, C., & Ward, D. (2017). Hypoactive delirium. BMJ : British Medical Journal (Online), 357. doi:http://dx.doi.org/10.1136/bmj.j2047

Inouye, S. K., Westendorp, R. G., & Saczynski, J. S. (2014). Delirium in elderly people. Lancet, 383(9920), 911-922. doi:10.1016/s0140-6736(13)60688-1

Kim, D. W., Kim, H. K., Bae, E. K., Park, S. H., & Kim, K. K. (2015). Clinical predictors for delirium tremens in patients with alcohol withdrawal seizures. American Journal of Emergency Medicine, 33(5), 701-704. doi:10.1016/j.ajem.2015.02.030

Kozak, H. H., Uguz, F., Kilinc, I., Uca, A. U., Serhat Tokgoz, O., Akpinar, Z., & Ozer, N. (2017). Delirium in patients with acute ischemic stroke admitted to the non-intensive stroke unit: Incidence and association between clinical features and inflammatory markers. Neurologia i Neurochirurgia Polska, 51(1), 38-44. doi:10.1016/j.pjnns.2016.10.004

Lipowski, Z. J. (1983). Transient cognitive disorders (delirium, acute confusional states) in the elderly. American Journal of Psychiatry, 140(11), 1426-1436. doi:10.1176/ajp.140.11.1426

Lowery, E. M., Brubaker, A. L., Kuhlmann, E., & Kovacs, E. J. (2013). The aging lung. Clinical Interventions in Aging, 8, 1489-1496. doi:10.2147/CIA.S51152

Maldonado, J. (2008). Pathoetiological model of delirium: A comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. Critical Care Clinics, 24(4), 789-856, ix. doi:10.1016/j.ccc.2008.06.004

Michaud, C. J., Bullard, H. M., Harris, S. A., & Thomas, W. L. (2015). Impact of Quetiapine Treatment on Duration of Hypoactive Delirium in Critically Ill Adults: A Retrospective Analysis. Pharmacotherapy, 35(8), 731-739. doi:10.1002/phar.1619

Mulkey, M. A., Hardin, S. R., Olson, D. M., & Munro, C. L. (2018). Pathophysiology review: Seven neurotransmitters associated with delirium. Clinical Nurse Specialist, 32(4), 195-211. doi:10.1097/nur.0000000000000384

Mulkey, M. A., Roberson, D. W., Everhart, D. E., & Hardin, S. R. (2018). Choosing the Right Delirium Assessment Tool. Journal of Neuroscience Nursing, 50(6), 343-348.

doi:10.1097/jnn.0000000000000403

Nedergaard, H. K., Jensen, H. I., Stylsvig, M., Lauridsen, J. T., & Toft, P. (2016). Non-sedation versus sedation with a daily wake-up trial in critically ill patients recieving mechanical ventilation - effects on long-term cognitive function: Study protocol for a randomized controlled trial, a substudy of the NONSEDA trial. Trials, 17(1), 269. doi:10.1186/s13063-016-1390-5

Nguyen, D. N., Huyghens, L., Zhang, H., Schiettecatte, J., Smitz, J., & Vincent, J. L. (2014). Cortisol is an associated-risk factor of brain dysfunction in patients with severe sepsis and septic shock. Biomed Research International, 2014, 712742. doi:10.1155/2014/712742

Numan, T., Slooter, A., van der Kooi, A. W., Hoekman, A. M. L., Suyker, W. J. L., Stam, C. J., & van Dellen, E. (2017). Functional connectivity and network analysis during hypoactive delirium and recovery from anesthesia. Clinical Neurophysiology, 128(6), 914-924. doi:10.1016/j.clinph.2017.02.022

Peritogiannis, V., Bolosi, M., Lixouriotis, C., & Rizos, D. V. (2015). Recent Insights on Prevalence and Corelations of Hypoactive Delirium. Behavioural Neurology, 2015, 416792. doi:10.1155/2015/416792

Peterson, J. F., Pun, B. T., Dittus, R. S., Thomason, J. W., Jackson, J. C., Shintani, A. K., & Ely, E. W. (2006). Delirium and its motoric subtypes: A study of 614 critically ill patients. Journal of the American Geriatrics Society, 54(3), 479-484. doi:10.1111/j.1532-5415.2005.00621.x

Robinson, T. N., Raeburn, C. D., Tran, Z. V., Brenner, L. A., & Moss, M. (2011). Motor subtypes of postoperative delirium in older adults. Archives of Surgery, 146(3), 295-300. doi:10.1001/archsurg.2011.14

Rowe, A. S., Hamilton, L. A., Curtis, R. A., Davis, C. R., Smith, L. N., Peek, G. K., & Reynolds, V. W. (2015). Risk factors for discharge on a new antipsychotic medication after admission to an intensive care unit. Journal of Critical Care, 30(6), 1283-1286. doi:10.1016/j.jcrc.2015.08.009

Stransky, M., Schmidt, C., Ganslmeier, P., Grossmann, E., Haneya, A., Moritz, S., . . . Trabold, B. (2011). Hypoactive delirium after cardiac surgery as an independent risk factor for prolonged mechanical ventilation. Journal of Cardiothoracic and Vascular Anesthesia, 25(6), 968-974. doi:10.1053/j.jvca.2011.05.004

Todd, A., Blackley, S., Burton, J. K., Stott, D. J., Ely, E. W., Tieges, Z., . . . Shenkin, S. D. (2017). Reduced level of arousal and increased mortality in adult acute medical admissions: a systematic review and meta-analysis. BMC Geriatrics, 17(1), 283. doi:10.1186/s12877-017-0661-7

van den Boogaard, M., Schoonhoven, L., Evers, A. W., van der Hoeven, J. G., van Achterberg, T., & Pickkers, P. (2012). Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. Critical Care Medicine, 40(1), 112-118. doi:10.1097/CCM.0b013e31822e9fc9

van den Boogaard, M., Schoonhoven, L., van der Hoeven, J. G., van Achterberg, T., & Pickkers, P. (2012). Incidence and short-term consequences of delirium in critically ill patients: A prospective observational cohort study. International Journal of Nursing Studies, 49(7), 775-783. doi:10.1016/j.ijnurstu.2011.11.016

van Velthuijsen, E. L., Zwakhalen, S. M., Mulder, W. J., Verhey, F. R., & Kempen, G. I. (2017). Detection and management of hyperactive and hypoactive delirium in older patients during hospitalization: A retrospective cohort study evaluating daily practice. International Journal of Geriatric Psychiatry. doi:10.1002/gps.4690

Wan, R. Y., Kasliwal, M., McKenzie, C. A., & Barrett, N. A. (2011). Quetiapine in refractory hyperactive and mixed intensive care delirium: a case series. Critical Care (London, England), 15(3), R159. doi:10.1186/cc10294

Zhang, W., Hu, W., Shen, M., Ye, X., Huang, Y., & Sun, Y. (2016). Profiles of delirium and the clinical outcomes of patients who underwent coronary artery bypass grafting: a prospective study from China. Journal of Clinical Nursing, 25(5-6), 631-641. doi:10.1111/jocn.13089

Calendar of Events

2019:

- **The Movement Disorders Chapter Parkinson's Disease Education Day for Nurses**, 3rd June 2019, St Leonards, NSW. https://www.anna.asn.au/
- **ANNA Annual Conference**, 16-18th October, Wellington New Zealand. https://www.anna.asn.au/
- **2019 AANN Advances in Stroke Care Conference** 22-24th August Austin Texas
- **3rd Annual International Neuroscience Nursing Research Symposium (INNRS)**, 24-25th August Austin Texas

2020:

- **52nd Annual Educational Meeting Illuminating Opportunities in a Time of Change**, 18-21st April 2020, Orlando Florida

2021:

- **WFNN Congress**
  20-23rd July, Darwin Australia**.**
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Successful applicants presenting an oral paper **must** submit a full written paper to be published in the *Australasian Journal of Neuroscience* as part of their award requirements before the end of the next financial year . The successful applicants name will be forwarded to the Journal Editor for follow-up.

The Louie Blundell Prize

This prize is in honour of our colleague Louie Blundell and will be awarded for the best neuroscience nursing paper by a student submitted to the Australasian Neuroscience Nurses Association (ANNA) for inclusion in the Australasian Journal of Neuroscience by the designated date each year. The monetary value of the prize is AUD$500.

Louie Blundell, was born in England, and although she wanted to be a nurse she had to wait until after World War II to start her training as a mature student in her late twenties. Later she and her family moved to Western Australia in 1959. She worked for a General Practice surgery in Perth until a move to the Eastern Goldfields in 1963. Subsequently, she worked at Southern Cross Hospital and then Meriden Hospital. During this time she undertook post basic education to maintain her currency of knowledge and practice, especially in coronary care.

Louie was also active in the community. She joined the Country Women's Association and over the years held branch, division and state executive positions until shortly before her death in 2007. She was especially involved in supporting the welfare of students at secondary school, serving on a high school hostel board for some time.

She felt strongly that education was important for women and was a strong supporter and advocate of the move of nursing education to the tertiary sector, of post graduate study in nursing and the development of nursing scholarship and research, strongly defending this view to others over the years.

For further details and criteria guidelines please visit the ANNA website at **www.anna.asn.au**

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