KANSAS JOURNAL of MEDICINE

A Case of Persistent Postictal and Inter-ictal Delirium

Vy Le, D.O.[1,2], Kylee Wollard[1], Ricky W. Lee, M.D.[3,4], Kamalakar Surineni, M.D.[1,2]
[1]University of Kansas School of Medicine-Wichita, Wichita, KS
[2]Department of Psychiatry and Behavioral Sciences
[3]Department of Internal Medicine
[4]Ascension Via Christi, Wichita, KS

Received April 19, 2023; Accepted for publication July 12, 2023; Published online Aug. 24, 2023
https://doi.org/10.17161/kjm.vol16.20116

INTRODUCTION

Delirium is a sudden change in baseline brain function that causes a disturbance in attention, awareness, and memory that typically fluctuates in its course. Certain medications, infections, electrolyte abnormalities, and epileptic activity can trigger delirium.[1] Older adults and individuals with pre-existing neurological diseases are at an increased risk. Delirium is a challenging condition to manage and affects up to 50% of older hospitalized patients.[2] The clinical presentation includes abnormal changes in an individual's consciousness and thought processes and difficulty focusing and maintaining orientation.[3] Uncovering the inciting event and alleviating distressing symptoms are the focus of management. Initial evaluation includes laboratory blood and urine, and possibly cerebrospinal fluid testing, brain imaging, and electroencephalography (EEG).

While delirium typically improves over time, persistent delirium is associated with worse outcomes and increased morbidity and mortality.[4] Certain factors like sepsis, electrolyte abnormalities, and epileptic activity increase the likelihood of developing persistent symptoms of delirium.[5] A significant proportion of older adults with delirium were found to have epileptic activity and suggested the utility of continuous EEG in this population.[6] Additionally, immune-checkpoint inhibitor (ICI) therapies, such as pembrolizumab, are associated with the complication of neurotoxicity and the development of encephalitis.[7] Pembrolizumab works by binding to the protein PD-1 on the surface of certain cancer cells and is used to treat multiple cancers, including triple-negative breast cancer. The potential for pembrolizumab to induce a state of chronic epileptogenicity has been reported previously.[8] While neurotoxicity is a known complication of ICIs, there were limited data surrounding the occurrence of status epilepticus, the development of persistent delirium, and how to guide management.

In this case report, a 69-year-old female with a history of resected bifrontal meningioma and breast cancer treated with pembrolizumab presented with status epilepticus and subsequently developed persistent delirium. This case illustrated the multifactorial nature of persistent delirium and the contribution of prior brain dysfunction, pembrolizumab use, and infectious insults.

CASE REPORT

A 69-year-old female was transferred to the senior behavioral health unit (SBHU) for delirium after a prolonged admission to the neurocritical care unit (NCCU). Her history was significant for a resected olfactory groove skull base bifrontal meningioma, as shown in Figure 1, breast cancer in remission, and hypothyroidism. She received her most recent infusion of pembrolizumab for breast cancer adjuvant treatment two days before admission to the NCCU. In addition, psychiatric history was significant for the development of delirium-related visual hallucinations following surgical resection of the meningioma, and they were managed successfully with quetiapine. Before this admission, she lived with her husband and was independent in all her activities of daily living (ADLs). There was no report of prior seizures or family history of seizures.

Her initial presentation to the NCCU included altered mental status, an acute aphasia, and recurrent right facial twitching. Magnetic resonance imaging (MRI) brain showed chronic bifrontal encephalomalacia (Figure 1) secondary to the resection of her previous meningioma. However, no acute ischemia was seen on the MRI brain. Continuous video EEG subsequently was started and recorded left frontal status epilepticus (Figure 2). Seizures were treated with intravenous midazolam, levetiracetam, fosphenytoin, and valproic acid. Her course was complicated by septic shock in the setting of right lower lobe pneumonia, necessitating vasopressor support and mechanical ventilation for two weeks in the NCCU. She remained lethargic even after hemodynamic stability was achieved.

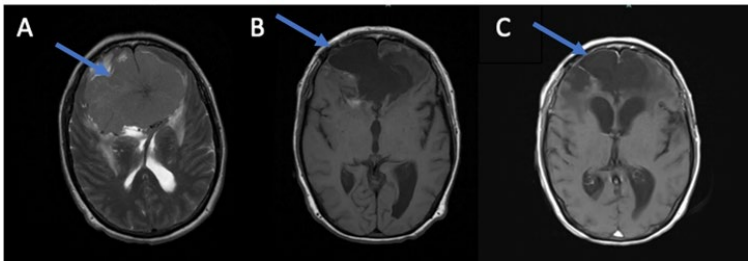

Figure 1. MRI showed: A) Large extra-axial mass centered in the anterior interhemispheric fissure exerting marked mass effect on the bilateral frontal lobes anteriorly and the anterior right temporal lobe. Mass was found to be a skull base meningioma and was subsequently resected. B) Postsurgical changes of mass resection from the anterior cranial fossa. No mass-like enhancement was seen to suggest residual tumor. Linear enhancement along the dura overlying the anterior left frontal lobe may represent continued postsurgical changes. C) Previous operative changes of frontal craniotomy with resection of a prior large interhemispheric meningioma. Postsurgical encephalomalacia, gliosis, and volume loss are unchanged from prior exam.

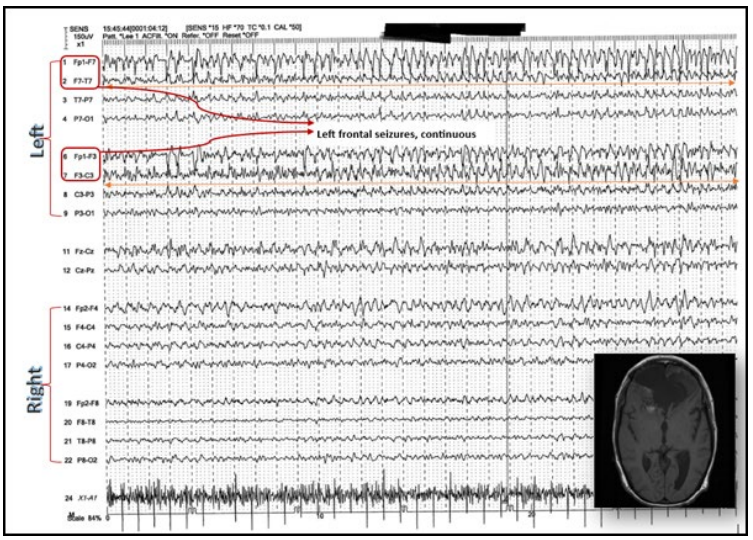

Figure 2. Excerpt of the first 30 seconds of continuous EEG recording. (Courtesy of Dr. Ricky Lee, neurology department at Via Christ St. Francis, Wichita).

Cerebral spinal fluid (CSF) evaluation was unrevealing. Due to concerns of oversedation, her antiepileptic regimen was tapered to include only levetiracetam 500 mg twice daily (BID) and lacosamide 200 mg BID. She became more alert and responsive and could follow simple commands and use a writing pad. However, following extubation, her course was complicated by the development of delirium with agitation and delusions, which prompted her transfer to senior behavioral health.

On admission to the SBHU, she remained confused in the setting of delirium; additional history was collected from medical records and collateral information provided by her husband. Initial examination revealed a frail elderly female alert and oriented to self, month, year, and location. Her remote memory was fair, and she was able to recount her past medical history. Her recent history was poor, and she did not know why she was hospitalized. She also perseverated on delusional beliefs surrounding the idea that her husband had been deceased for several years. She had leukocytosis with abundant immature neutrophils that were concerning for infection. However, no source could be identified, and the leukocytosis was resolved with empiric antibiotic treatment. Her clinical picture shifted from hyperactive delirium with agitation to hypoactive delirium with significant lethargy.

Treatment. During the hospital course, the patient failed three trials of antipsychotics, quetiapine, haloperidol, and risperidone; the last two agents were discontinued due to concern for decreased responsiveness and catatonic symptoms. Her antiepileptic regimen included initiation of lacosamide. She also failed the first trial of mirtazapine because of oversedation, but tolerated the second trial. Cognitive enhancer, memantine, was added, titrated to maximum daily dose with minimal benefits.

Outcome. Her mental status continued to fluctuate with minimal overall improvement. Further investigative studies were done over the course of her hospitalization, including blood cultures, cerebrospinal fluid analysis, meningitis/encephalitis panel, paraneoplastic antibody testing, cryptococcal antigen testing, HIV and syphilis antibody screens, and urinalysis. Following the resolution of sepsis, all studies were unrevealing for a cause of her persistent delirium. Repeat EEG evaluation demonstrated generalized background slowing without epileptogenic abnormalities.

Unfortunately, her delirium persisted over the next three months without significant improvement. She continued to need extensive nursing support regarding transferring, toileting, and feeding herself. Occasionally, she was alert and oriented to herself, location, and year, and she could hold short conversations before perseverating on a particular topic again. However, most days, she remained minimally interactive and oriented to herself, and her poor responsiveness rendered her unable to participate in the interview or exam. Figure 3 shows a timeline of this patient's assessment and treatment.

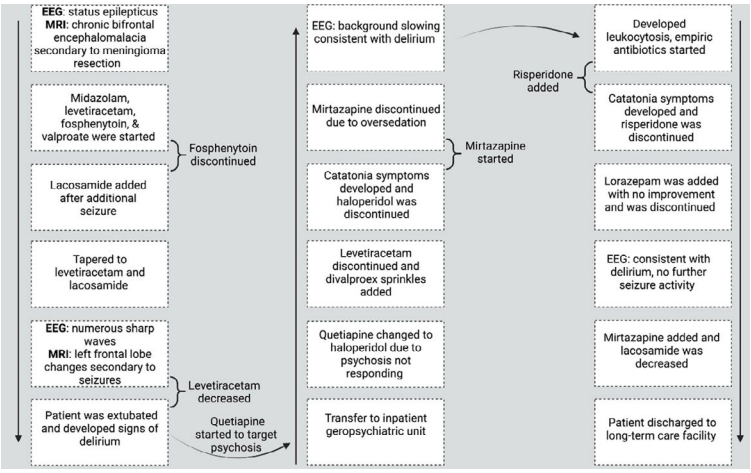

Figure 3. Timeline of patient's assessment and treatment. (Created with BioRender.com)

DISCUSSION

This case report illustrated the challenges of identifying definitive etiologies for persistent delirium, given the sophisticated interaction between various predisposing and precipitating factors, posing barriers to effective management, the need for which was highlighted by the high prevalence and increased morbidity and mortality. Indeed, 18 reports (involving 1,322 older hospital patients with delirium) compiled in a systematic review in 2009 suggested that persistent delirium at discharge, one, three, and six months comprised 44.7% (95% CI 26.8%, 63.7%), 32.8% (95% CI 18.4%, 47.2%), 25.6% (95% CI 7.9%, 43.4%) and 21% (95% CI 1.4%, 40.6%), respectively.[2] Additionally, more adverse outcomes, in terms of mortality, nursing placement, cognition and functional capacities, consistently were reported in persistent delirium.

One-third of 412 subjects with an average age of 84 and Mini-Mental State Examination (MMSE) of 12.5 from eight Boston area skilled nursing facilities specializing in post-acute delirious care had persistent delirium.[4] It was concluded that the cumulative one-year mortality was 39%, and there was 2.9% increase in one-year mortality in subjects with persistent delirium, when corrected for age, gender, comorbidity, functional status, and present of premorbid dementia. Notably, functional impairment leading to decreased ability to tend to Instrumental Activities of Daily Living (ADL) which is among the important prognostic indicators in persistent delirium.[4,9]

It was likely that in our case, the patient's prolonged delirious course rendered her fully dependent on ADLs in light of significant limitation with mobility and frailty, contributory to poor outcomes. Based upon her premorbid functioning, frailty appeared to be the sequela of persistent delirium and proved to be independent predictor of adverse outcomes. This was consistent with the findings of a 2018 prospective study which also revealed an inverse relationship between frailty and impacts of delirium on mortality.[10] In other words, delirium was found to have greatest implications in risk of death in fittest patients, likely explained by typically more serious insults for precipitation of delirium in patients with larger cognitive and physiological reserves. The study emphasized the presence of a distinct neurological determinant, harkening back to various neurological detriments our patient sustained, most prominently, history of bifrontal meningioma resection with encephalomalacia and status epilepticus.

A retrospective study investigating 177 patients with delirium identified 15% with epileptic activity on EEG, one-fifth comprising nonconvulsive status epilepticus.[6] Another prospective multicenter randomized controlled study revealed a 7% increase in prevalence of delirium in mechanically-ventilated patients with observable seizures and status epilepticus on EEG.[11] Both findings suggested a significant contribution of seizures to the evolution of delirium.[6,11] In another study, nonconvulsive status epilepticus and interictal discharges were found in 12% and 30% of elderly delirium patients, respectively, irrespective of the etiologies.[12] It can be theorized that the presence of an epileptic focus in the cortex promoted encephalopathy via widespread neuronal metabolism alteration, specifically in the functions of the cholinergic, serotonergic, and catecholaminergic systems in subcortical areas, which can produce diffuse cortical hypoactivity.[13] Both animal and human models demonstrated linkage between the affected and connected regions through synaptic changes, for which there is direct electrophysiological evidence via electrocorticography and motor mapping, which allowed visualization of changes induced by an intractable focal epileptic discharges.[13-15]

The clinical picture in our patient was obfuscated by the presence of sepsis secondary to pneumonia, as well as electrolyte (hypocalcemia and hypomagnesemia) and thyroid hormone abnormalities, all of which are well-known risk factors for seizures. Up to 20% of critically ill patients with sepsis developed seizures presented atypical in elderly populations.[5] The cytokine, IL-1β, creates an imbalance of N-methyl-D-aspartate (NMDA) and γ-amino-butyric-acid (GABA) activities, mediating calcium influx into neurons, synergizing with increased permeability of blood brain barrier for potentiation of neuronal excitability.[5,16]

Our patient highlighted the laborious process of elucidating the weights of relevant factors in persistent delirium. It was difficult to determine whether seizures caused encephalopathy or sepsis-associated encephalopathy predisposed the patient to epileptiform discharges in the backdrop of post-op structural changes. Additionally, there was a temporal relation between her pembrolizumab infusion and onset of seizures, and it was unclear whether pembrolizumab was culpable of unremitting epileptic activities.

The proposed pathophysiology is the induction of a chronic state of epileptogenicity similar to autoimmune epilepsy.[8] Regardless of morphologies, status epilepticus is associated with cerebral hypoxia, one of the aggravating factors in prolonged delirium.[9,17,18] The concomitant seizures in sepsis is a potential marker of brain dysfunction that has significant prognostic values.[6,18] Although the precise contribution of individual factors remains elusive, it a confluence was likely of all predictors for poor outcomes in our patient, not to mention the necessity of anticonvulsants that could exacerbate cognitive impairment. Levetiracetam might not be the ideal choice due to its implication in neuropsychiatric disturbances such as hallucinations, delusions, agitation with 13.8% of patients treated for focal epilepsy experienced psychiatric treatment-emergent adverse events, and that there was comparable efficacy of phenytoin, valproic acid, and levetiracetam in management of status epilepticus.[19,20]

In our case, cross-titration from levetiracetam to valproic acid saw improvement in psychiatric symptoms but no clinical change overall. According to the expert consensus guideline, valproic acid is considered for managing combativeness with high risk of physical aggression, further supporting the adjustment of her antiepileptic regimen, which our patient tolerated relatively well.[21] Her course of illness was compounded by the intolerability to antipsychotics, the benefits of which in delirium remain controversial, given the most severe or harmful adverse drug reactions were observed in 18% of patients in a systematic review of the literature regarding pharmacologic therapy for ICU delirium.[22] Haloperidol, a commonly used drug, did not show any clinical superiority over placebo, whereas quetiapine was found to have yielded faster resolution of delirium. Taking into account her previous quetiapine trial, it was possible that quetiapine could have precluded extrapyramidal effects and catatonic symptoms and engendered better outcomes. However, it remained questionable whether antipsychotics are recommended in the first place when delirium is linked to epileptic activity, and whether treatment strategies should be centered around anticonvulsant therapy.

Long-term cognitive impairment is one known repercussion of delirium, yet there was little research into the use of cognitive enhancers in such cases.[23] Memantine, an NMDA antagonist, is indicated to treatment of moderate-to-severe dementia of Alzheimer's type, and there was also evidence of significant efficacy in global functioning in vascular dementia with no difference in the number of people discontinuing memantine due to adverse effects.[24,25] Because there were available case reports of improvement in prolonged delirium with catatonia after memantine, our patient was trialed on memantine for cognition, while ensuring supplementation with folic acid and thiamine.[26,27] Unfortunately, in our patient, memantine proved to be of little clinical benefit; there had been minimal change until the patient was discharged to long term care.

CONCLUSIONS

The persistence of delirium, accompanied with profound morbidity and mortality, in its multifactorial nature, entail significant difficulties in prompt diagnosis and effective management. Sepsis and concurrent epileptic activity, specifically status epilepticus, are among poor prognostic markers, in which case, resolution of underlying etiologies did not translate into restoration of baseline cognitive and functional capacities. The efficacy of cognitive enhancers in prolonged delirium could be an area of active research. Further exploration into the overlap of symptoms between delirium and nonconvulsive status epilepticus could enhance understanding and help tackle this treatment conundrum.

REFERENCES

[1] Pisani MA, Murphy TE, Van Ness PH, Araujo KL, Inouye SK. Characteristics associated with delirium in older patients in a medical intensive care unit. Arch Intern Med 2007; 167(15):1629-1634. PMID: 17698685.
[2] Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: A systematic review of frequency and prognosis. Age Ageing 2009; 38(1):19-26. PMID: 19017678.
[3] McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: Occurrence and clinical course in older patients. J Am Geriatr Soc 2003; 51(5):591-598. PMID: 12752832.

[4] Kiely DK, Marcantonio ER, Inouye SK, et al. Persistent delirium predicts greater mortality. J Am Geriatr Soc 2009; 57(1):55-61. PMID: 19170790.
[5] Alessandri F, Badenes R, Bilotta F. Seizures and sepsis: A narrative review. J Clin Med 2021; 10(5):1041. PMID: 33802419.
[6] Naeije G, Bachir I, Gaspard N, Legros B, Pepersack T. Epileptic activities are common in older people with delirium. Geriatr Gerontol Int 2014; 14(2):447-451. PMID: 23910220.
[7] Wei D, Zhou DJ, Datta P, Taraschenko O. Recognizing encephalopathy in immune checkpoint inhibitor therapy: A single-center experience. Cancer Med 2021; 10(9):2978-2986. PMID: 33660430.
[8] Takebayashi Y, Neshige S, Hayashi T, et al. A case of repetitive seizures following immune checkpoint inhibitor therapy as a feature of autoimmune encephalitis. Epileptic Disord 2021; 23(5):733-738. PMID: 34519645.
[9] Dasgupta M, Hillier LM. Factors associated with prolonged delirium: A systematic review. Int Psychogeriatr 2010; 22(3):373-394. PMID: 20092663.
[10] Dani M, Owen LH, Jackson TA, Rockwood K, Sampson EL, Davis D. Delirium, frailty, and mortality: Interactions in a prospective study of hospitalized older people. J Gerontol A Biol Sci Med Sci 2018; 73(3):415-418. PMID: 29099916.
[11] Eskioglou E, Iaquaniello C, Alvarez V, et al. Electroencephalography of mechanically ventilated patients at high risk of delirium. Acta Neurol Scand 2021; 144(3):296-302. PMID: 33950516.
[12] Sambin S, Gaspard N, Legros B, Depondt C, De Breucker S, Naeije G. Role of epileptic activity in older adults with delirium, a prospective continuous EEG study. Front Neurol 2019; 10:263. PMID: 30941098.
[13] Lado FA, Rubboli G, Capovilla G, Avanzini G, Moshé SL. Pathophysiology of epileptic encephalopathies. Epilepsia 2013; (54 Suppl 8):6-13. PMID: 24571111.
[14] Henderson AK, Galic MA, Fouad K, Dyck RH, Pittman QJ, Teskey GC. Larger cortical motor maps after seizures. Eur J Neurosci 2011; 34(4):615-621. PMID: 21749495.
[15] Lado FA, Legatt AD, LaSala PA, Shinnar S. Alteration of the cortical motor map in a patient with intractable focal seizures. J Neurol Neurosurg Psychiatry 2002; 72(6):812-815. PMID: 12023433.
[16] Han P, Trinidad BJ, Shi J. Hypocalcemia-induced seizure: Demystifying the calcium paradox. ASN Neuro 2015; 7(2):1759091415578050. PMID: 25810356.
[17] Somjen G. (Ed.) Mechanisms of Cerebral Hypoxia and Stroke. New York: Plenum Press, 1988. ISBN: 9871468455649.
[18] Kooken RWJ, van den Berg M, Slooter AJC, Pop-Purceleanu M, van den Boogaard M. Factors associated with a persistent delirium in the intensive care unit: A retrospective cohort study. J Crit Care 2021; 66:132-137. PMID: 34547553.
[19] Chung S, Ceja H, Gawłowicz J, McShea C, Schiemann J, Lu S. Levetiracetam extended release for the treatment of patients with partial-onset seizures: A long-term, open-label follow-up study. Epilepsy Res 2016; 120:7-12. PMID: 26716580.
[20] Mundlamuri RC, Sinha S, Subbakrishna DK, et al. Management of generalised convulsive status epilepticus (SE): A prospective randomised controlled study of combined treatment with intravenous lorazepam with either phenytoin, sodium valproate or levetiracetam--Pilot study. Epilepsy Res 2015; 114:52-58. PMID: 26088885.
[21] Alexopoulos GS, Jeste DV, Chung H, Carpenter D, Ross R, Docherty JP. The expert consensus guideline series. Treatment of dementia and its behavioral disturbances. Introduction: Methods, commentary, and summary. Postgrad Med 2005; Spec No:6-22. PMID: 17203561.
[22] Korenoski A, Li A, Kane-Gill SL, Seybert AL, Smithburger PL. Pharmacologic management of delirium in the ICU: A review of the literature. J Intensive Care Med 2020; 35(2):107-117. PMID: 30309280.
[23] Ali S, Patel M, Jabeen S, et al. Insight into delirium. Innov Clin Neurosci 2011; 8(10):25-34. PMID: 22132368.
[24] Jin BR, Liu HY. Comparative efficacy and safety of cognitive enhancers for treating vascular cognitive impairment: Systematic review and Bayesian network meta-analysis. Neural Regen Res 2019; 14(5):805-816. PMID: 30688266.
[25] McShane R, Westby MJ, Roberts E, et al. Memantine for dementia. Cochrane Database Syst Rev 2019; 3(3):Cd003154. PMID: 30891742.
[26] Brown GD, Muzyk AJ, Preud'homme XA. Prolonged delirium with catatonia following orthotopic liver transplant responsive to memantine. J Psychiatr Pract 2016; 22(2):128-132. PMID: 27138082.
[27] Roy K, Warnick SJ, Balon R. Catatonia delirium: 3 cases treated with memantine. Psychosomatics 2016; 57(6):645-650. PMID: 27692655.

Keywords: delirium, seizures, encephalomalacia, meningioma