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Case Report

Levetiracetam Associated Delirium in an Adult Male – A Case Report

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Abstract

Delirium is a potentially life-threatening neuropsychiatric medical emergency, especially in the elderly. Unrecognized or untreated or inappropriately treated delirium may lead to significant morbidity or mortality. Medication-induced delirium is not uncommon in elderly patients with complex medication regimens. Medications are one of the most common precipitating factors for triggering delirium and often one of the most easily correctable. A case of acute onset visual hallucinations associated with levetiracetam addition to an extensive medication regimen in an elderly male with a complex medical and psychiatric history is presented. A Naranjo scale assessment indicated that the acute delirium was in the probable range, in terms of its association with levetiracetam. The patient had multiple risk factors (age, multiple medical comorbidities, history of pre-existing cognitive impairment, treatment with multiple medications known to be risk factors for delirium) predating addition of the levetiracetam, however the addition appeared consistent with the time course of the delirium onset. Levetiracetam prescribing information reports psychotic symptoms in 1% of treated adults versus 0.2% in placebo. New onset psychiatric/behavioral side effects related to levetiracetam were noted in 15.7% of 221 patients in a study of newer AEDs in 2007; greater than those seen with gabapentin, lamotrigine, topiramate, zonisamide, but similar to tiagabine. Anger and aggression were more frequently reported with levetiracetam than other AEDs (49% versus 39% compared to 7% in controls).While delirium is typically multifactorial in etiology, increased medication burden, particularly involving anticholinergics, benzodiazepines, and opiates, among others, is a significant risk factor. With increased use of levetiracetam for neurological indications due to efficacy, perceived safety, and cost effectiveness (generic, minimal monitoring), clinicians should be aware of potential adverse psychiatric manifestations with this agent.

ABBREVIATIONS

AED: Antiepileptic Drug, BMI: Body Mass Index, BNP: Brain Natriuretic Peptide , BUN: Blood Urea Nitrogen ,CBC: Complete Blood Count, CNS: Central Nervous System, Crcl: Creatinine Clearance ,DSM-5: Diagnostic And Statistical Manual Of Mental Disorders, 5th Edition ,EEG: Electroencephalogram ,ECG: Electrocardiogram ,FBG: Fasting Blood Glucose, Hgba1c: Hemoglobin A1C,IBW: Ideal Body Weight, LFT: Liver Function Tests ,PE: Physical Exam, PO: Per Oral ,PRN: As Needed ,PTA: Prior To Admission ,Q2: Every Two,Q4: Every Four ,TSH: Thyroid Stimulating Hormone

INTRODUCTION

Delirium, as a neuropsychiatric syndrome, is a disturbance of awareness and attention, along with changes in cognition or perceptual disturbances [1-4]. Medication-induced delirium is not uncommon in elderly patients with complex medication regimens, especially in those regimens with increased anticholinergic burden [2, 5, 6]. As contrasted with dementia, delirium evolves rapidly over hours to days and may resolve rapidly with appropriate treatment [4, 7]. The degree of impairment may fluctuate throughout. As dementia and pre-existing cognitive impairment are risk factors for developing delirium, there may be overlap (delirium superimposed on dementia) and thus it may be difficult for clinicians to distinguish between the two (dementia versus delirium) on initial presentation[4,7]. Known risk factors for delirium include advanced age, pre-existing dementia, certain medications, previous neurologic illness, and acute infectious disease, among others (Table 1) lists a more comprehensive set of delirium risk factors) [2,3,8].Delirium is more commonly seen in the elderly, with estimates that up to 30-40% of hospitalized

elderly patients have delirium, in particular in post-surgical and ICU settings [9]. Further, there is a belief among many clinicians that delirium is often under-recognized in these inpatient settings, and thus untreated or treated inappropriately [3].

Medications are one of the most common precipitating factors for triggering delirium and often one of the most easily correctable [2, 8]. It has been estimated that up to 12-39% of delirium incidents in the elderly are related to medication use [2, 10-12]. The authors present a case of acute mental status changes associated with a recent medication addition to an already impressive drug load in an elderly male.

Patient case

A 66-year-old Caucasian male with a complex medical and psychiatric history was referred from a skilled nursing facility to the medical-psychiatric inpatient unit with acute onset of visual hallucinations (monsters, horses). Due to multiple medical and psychiatric comorbidities (Table 2), the patient had accumulated an impressive medication regimen (Table 3) at the time of admission. Three weeks (21 days) prior to admission, levetiracetam therapy (500mg PO BID) was initiated by a local acute care hospital emergency department for abnormal neurologic activity (multiple recent episodes of tremors of upper and lower extremeties) with unremarkable EEG, with four episodes occurring on the morning prior to being seen in the emergency department. An MRI of the head prior to admission confirmed the presence of an old small thalamic infarct. The seizure episodes were reported by the skilled nursing facility staff to be upper extremity jerks with patient slumping over for 30-60 seconds in duration, with the patient nonresponsive during the episode, and a brief post-actual period of confusion. The patient described seeing “flashing lights” and having sensations of “electric shock” and “skin crawling” of the scalp. Blood glucose testing at the time of the episodes prior to admission were normal to elevated (episodes not hypoglycemia related) per documentation available from the nursing facility at the time of admission. Prior to sending the patient to the emergency department, clonazepam dosing was increased at the nursing facility from 0.5mg TID to 1mg TID in an attempt to address the abnormal neurologic episodes, however the patient became over sedated and the dose was decreased back to baseline due to concerns that his respiratory status would be further compromised.

Table 1: Clinical Risk Factors Commonly Associated with Delirium.

Increased age	Medications (class)
Dementia diagnosis at baseline Prior brain disease or history of TBI Loss of/impairment of vision or hearing Acute infection Major stress Poor nutrition/hydration Substance use disorder Lack of sleep Urinary incontinence or retention	-Anticholinergics, anti-parkinsons -Sedatives (benzodiazepines, opiates) -Antipsychotics, corticosteroids Medications- (number) - Polypharmacy - Increased medication burden (i.e. increased numbers of medications- suggested threshold of >=9 chronic medications or >= 12 doses of medication per day)

TBI = traumatic brain injury

Table 2: Patient Medical/Psychiatric History.

Mood disorder	Degenerative disc disease
Psychosis with delirium	Peripheral vascular disease
Cognitive disorder	Hypothyroidism
Peripheral neuropathy	Chronic headaches
Type II diabetes mellitus	Obstructive sleep apnea
Morbid obesity (BMI 47)	Seizure-like activity
Chronic kidney disease (CrCl 66ml/min)	History of polio v. post polio
Chronic pain syndrome	Cerebrovascular accident – old infarct of thalamus noted on MRI (confirmed 1 month PTA)
Encephalopathy (8 months PTA)	
Peripheral edema	
Anemia	History of urinary retention
Impaired mobility	Benign prostatic hypertrophy

BMI = body mass index , CrCl = creatinine clearance, PTA = prior to admission

Table 3: Medications on Admission and Subsequent Modifications.

cetaminophen-hydrocodone 10/325 mg 5 times per day and PRN q2h[1]	Metformin 1000 mg BID
Gabapentin 600 mg TID[2]	Insulin glargine 36 units SC every morning
Levetiracetam 500 mg BID[3]	Insulin aspart 12 units SC before breakfast
Duloxetine 60 mg BID	Insulin aspart 15 units SC before lunch
Clonazepam 0.5 mg TID	Insulin glargine 46 units SC with supper
Fentanyl 50 mcg transdermal patch daily	Insulin aspart 15 units SC with supper
Finasteride 5 mg daily	Aspirin 81 mg daily
Tamsulosin 0.8 mg daily at 2pm daily	Furosemide 40 mg daily
Diphenhydramine 50 mg q6h PRN[4]	Lisinopril 5 mg daily
Ipratropium and albuterol 0.5 mg/2.5 mg inhaled QID	Clopidogrel 75 mg daily
Oxygen 2 L continuously	Gentamycin topical ointment BID
CPAP use at bedtime	Nystatin topical powder TID
Timolol 1 drop each eye BID	Saline nasal spray 2 sprays each nostril BID PRN
Travoprost 0.004% 1 drop each eye at night	Ascorbic acid 500 mg TID
Docusate and senna 50 mg/8.6 mg 2 tablets at bedtime	MVI daily
	[1] changed to Q4H PRN only- upon admission
	[2] decreased to 400mg TID
	[3] tapered to discontinuation
	[4] discontinued on admission

CPAP = continuous positive airway pressure; MVI = multi-vitamin; L = liters; PRN = as needed; BID = twice daily; TID = three times daily; QID = four times daily; Q2h = every 2 hours; Q4h = every 4 hours; SC = subcutaneously

The patient reported visual hallucinations and worsening mood lability/anxiety corresponding to initiation of levetiracetam and began intermittently refusing this medication prior to the inpatient admission, as the patient attributed his mental status changes to levetiracetam. During the admission interview, the patient was somnolent and reported pain 8/10 despite aggressive pain management pharmacotherapy. Hallucinations remained present at the time of admission. According to available records, allergy history included amoxicillin/clavulanate, pregabalin, methadone, and morphine, however the exact nature of these allergies was not determined. He had a reported history of constipation and urinary retention, however bowel and bladder elimination was ruled out as a present contributor to the mental status changes.

Patient mental/Physical status

The patient was somnolent and apathetic with repeated dozing during the initial team interview. This interview occurred the morning after the admission on the previous evening. The patient was oriented to person only, and exhibited short-term memory deficits. He reported pain intensity as 8/10 despite medications. He reported that his mood was depressed and presented with slowed psychomotor function. The patient was not independently ambulatory, requiring a wheelchair for mobility. There was 3+ pitting edema noted bilaterally and stasis ulcers as well as wounds noted on the lower lateral left and right legs, likely from the wheelchair. Lower extremeties were to be elevated during the day; however these instructions were not consistently followed. The patient reported numbness and decreased sensation in both feet. The initial impression was dementia with acute delirium possibly related to medication. Vital signs (BP, pulse, temperature, respirations, O_2 saturation) were unremarkable at admission. Baseline lab studies on admission, including CBC, electrolytes,BNP, ECG, BUN, urinalysis, and LFTs were within normal range despite the presence of multiple medical conditions.Creatinine was 1.3 (calculated CrCl 54 ml/minute via Cockroft-Gault for IBW). TSH was reported as 0.79 mIU/L (0.4.4.0 mIU/L). FBG was 137 on admission (HgBA1c 9.1), with FBG ranging from 137-205 during admission. Substance abuse history was unclear as the patient refused to respond to the question, however the patient was a current smoker PTA. Visual hallucinations continued to be present at the time of the initial admitting interview and PE.

Treatment plan

After patient interview, physical examination, and work-up, the team elected to discontinue levetiracetam – tapering over 3 days (with the final dose given on the day prior to discharge). A trough levetiracetam level was found to be 14mcg/ml (5-30 mcg/ml) on the morning after admission. The patient admitted that he was intermittently refusing levetiracetam doses prior to admission, as he felt that this medication was related to the onset of his delirium. The medication regimen itself presented many risk factors for medication related delirium (multiple medications, opioid polypharmacy, presence of anticholinergic burden), however the addition of levetiracetam corresponded in a temporal manner to the onset of delirium and no other medication changes had been made in this timeframe. Further, in terms of providing anti-epileptic drug coverage, divalproex sodium extended release was initiated (Depakote ER) at dose of 750 mg PO at bedtime, then titrated up to 1000 mg PO at bedtime by discharge. Divalproex was chosen over carbamazepine due to being a broad spectrum AED with lesser risk of drug-drug interactions with the complex medication regimen. The patient had been treated with carbamazepine and zonisamide in the past, however the medication was tapered to discontinuation for reasons that were unclear from the medical record information available. The patient stated that these agents were stopped at his request “because the tremors stopped”. Other medication changes were to discontinue diphenhydramine (PRN) due to its anticholinergic potential, switched acetaminophen-hydrocodone from 5 time daily scheduled administration as well as Q2 hours PRN to Q4 hours PRN only, then lastly, the gabapentin dosage was decreased by 600mg/day due to somnolence noted at the time of admission (Table 3).

Patient outcome

By admission day two, the patient was oriented to person, place, and time and no longer reported visual hallucinations. He was much less somnolent as well. The patient reported no visual hallucinations on dival proex sodium extended release therapy. By the date of discharge, the patient on interview was more alert and awake/interactive/engaged. A valproic acid level drawn on date of discharge and was slightly sub therapeutic (48mcg/mL). The therapeutic range is 50-100 mcg/mL, however a full 5 days had not elapsed since initiation, and we may not have yet reached steady state, the patient was clinically stable, therefore the dose was not adjusted. The patient received only two doses of acetaminophen-hydrocodone per day during the hospital stay. A mini-mental status examination was administered on day three of the admission with a score of 25/30. At this time, significant cognitive clearing had already occurred.

The Naranjo scale, an adverse drug event probability assessment, classifies the probability that an observed adverse event is related to a specific medication therapy using a series of weighted questions. This method has been tested for internal validity with inter-rater reliability testing, and its probability scale has consensual, content, and concurrent validity [12]. Using the Naranjo scale, the event being investigated is assigned a probability category based upon total score of definite (score of 9 or more), probable (score of 5-8), possible (score of 1-4), or doubtful (score of 0) [12]. A Naranjo scale assessment was completed for this potential adverse event, with a total score of 5, indicating that the adverse event (acute delirium) was in the probable range, in terms of its relationship to the levetiracetam. As outlined above, this is a case with multiple potential etiologies for the delirium, however according to the skilled nursing facility reported information, the onset of the abnormal neurologic activity and the resulting treatment with levetiracetam were the only recent changes to this medical/psychiatric/neurologic status. On day six of the admission, the patient was discharged back to his prior skilled nursing facility without further seizure activity, hallucinations, or delusions observed/reported. At the time of discharge, the patient was pleasant, calm, and cooperative. Discharge psychiatric diagnosis was mood disorder NOS, delirium secondary to levetiracetam, and cognitive disorder NOS.

DISCUSSION

The DSM-5 notes that the delirium typically develops over a short period of time (usually hours to a few days), represents a change from baseline, and may fluctuate in severity during the course of the day [1]. Delirium is a disturbance in attention and awareness along with an additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception). Further, the disturbance cannot be better explained by another pre-existing, established, or evolving neurocognitive disorder and does not occur in the context of a severely reduced level of arousal, such as coma [1-3,9].It is necessary to collect a thorough history and perform a physical examination with laboratory assessments to determine if the disturbance is a direct physiological consequence of another medical condition,

substance intoxication, or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies[1-3,8,9]. In the present case, the delirium symptoms were preliminarily felt to be related temporally to a medication (levetiracetam), however other medications and medical comorbidities were present which clearly presented additional risk factors.

Delirium is a potentially life-threatening neuropsychiatric medical emergency, especially in the elderly [2, 3]. If unrecognized and/or untreated or inappropriately treated, it may lead to significant morbidity up to mortality [2, 9]. The present case exhibited multiple risk factors (age, multiple medical comorbidities, history of pre-existing cognitive impairment, treatment with multiple medications known to be risk factors for delirium) that predated the addition of the levetiracetam. The addition of this medication appeared to be consistent with the time course of the onset of the acute mental status changes observed. At the time of admission, the patient also was being treated with high dose opiates, multiple CNS depressants (gabapentin/clonazepam), and anticholinergics (diphenhydramine) which are also noted to be medication related risk factors for delirium (Table 1).

Levetiracetam is a novel AED, indicated for the adjunctive treatment of partial and generalized epilepsy. It's mechanism of action is unclear, oral absorption is rapid and complete, it is not extensively metabolized, with minimal drug interaction potential[14].Levetiracetam prescribing information reports psychotic symptoms in 1% of treated adults versus 0.2% in placebo, with symptom onset occurring the first week of treatment and resolving within 1-2 weeks of discontinuation[14]. A Pub-Med search of levetiracetam therapy related psychiatric adverse events going back 10 years (to 2003) identified one case control review of 553 subjects in which 6.9% stopped levetiracetam due to "behavioral abnormalities"[15] and another evaluation of 288 consecutive patients in which 37% reported negative or very negative behavioral changes (aggression, loss of self-control, restlessness, sleep problems)[16]. In the case-control study in which 38 of 553 patients discontinued levetiracetam due to behavioral adverse events, faster titration, history of psychiatric disorder, and diagnosis of symptomatic generalized epilepsy were apparent risk factors associated with the adverse events [15]. Three other case reports were identified in which patients experienced delirium, catatonia, and psychosis, respectively [17-19]. New onset psychiatric/behavioral side effects related to levetiracetam were noted in 15.7% of 221 patients in a study of newer AEDs in 2007; greater than those seen with gabapentin, lamotrigine, topiramate, zonisamide, but similar to tiagabine [20]. An unblinded, observational study of 418 patients with epilepsy and 41 control patients conducted in the United Kingdom found that 49% of the levetiracetam exposed patients reported anger as being a problem at least some of the time, compared to 39% treated with other AEDs (carbamazepine, lamotrigine, topiramate, zonisamide, phenytoin, phenobarbital), and 7% in the control group ($p = 0.042$) [21]. The presence of depression was reported at similar rates in the levetiracetam and "other AED" group (48 and 45%, respectively) [21]. Lastly, a case report highlighted the emergence of acute mania in a 58 year old female after levetiracetam therapy was initiated [22]. These reports substantiate that levetiracetam, despite being a very effective and typically safe AED, may be associated with psychiatric adverse effects in some patients.

There are multiple published reports which outline medications known to be risk factors for development of cognitive impairment in the elderly [2,3,5,8,9]. One of the most commonly cited is the "Beers List" which was initially developed in 1997 and most recently revised by the American Geriatrics Society in 2012 [5]. It is beyond the scope of this report to note all of the medications or medication classes which have been so implicated, however, in brief, medications with a high anticholinergic burden (diphenhydramine, tricyclic antidepressants, phenothiazine antipsychotic agents), opiates, and benzodiazepines are commonly implicated in being associated with delirium[5,8,9]. The present case has multiple such medications present (opiates, clonazepam, diphenhydramine), some of which (Table 3) were modified during the hospital stay in an effort to improve cognitive function.

Conservative management, including evaluation of the medication regimen and removal of the most likely offending medications, along with supportive therapy (vital signs, adequate hydration and nutrition support, clinical monitoring), as in this case, may be all that is required to restore the baseline level of cognitive functioning [8,9]. Early detection and intervention is critical to improving outcomes. Further, proactive steps aimed at prevention are worthwhile. Treatment is best directed at addressing the underlying causes (medications, infectious disease, etc) [2,3,9]. Pharmacologic treatment of delirium is recommended if patients are at risk of harming themselves or others. There are currently no FDA approved treatments specifically approved for delirium [2].Ongoing comprehensive medication management in the outpatient setting is essential in minimizing the potential adverse effect burden seen as medications for multiple comorbidities accumulate in the elderly patient [5,6, 9]. In particular, medications with significant anticholinergic burden, benzodiazepines, opiates, and dopamine agonists may be problematic [3,5, 8, 9]. The use of a primary care medical home and a single pharmacy for medication procurement are essential to allow for an ongoing proactive evaluation and screening of the medication regimen for such potential problems.

CONCLUSION

In this case, a temporal relationship existed between visual hallucinations onset and levetiracetam initiation, then hallucination resolution upon levetiracetam discontinuation. While delirium is typically multifactorial in etiology, increased medication burden, particularly with anticholinergics, benzodiazepines, and opiates, among others, is a common risk factor. With increased use of levetiracetam for neurological indications due to efficacy, perceived safety, and cost effectiveness (generic, minimal monitoring), clinicians should be aware of potential adverse psychiatric manifestations with this agent. Ongoing efforts directed at comprehensive medication management are essential to remove unnecessary medications which may be risk factors for delirium development.

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