

Ictal Catatonia in Autoimmune Encephalitis

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KEYWORDS: non-convulsive status epilepticus, bipolar disorder, anti-NMDA receptor encephalitis, catatonia, delirious mania

INTRODUCTION

Bipolar disorder (BD) type I is a chronic psychiatric illness characterized by episodes of mania and/or depressive symptoms. Its onset is classically diagnosed during early adulthood, but when a manic episode is observed in an older adult without a typical psychiatric history, it becomes particularly important to investigate for potential organic causes.¹

Delirious mania (DM)² manifests as an acute onset of manic signs and symptoms, accompanied by a waxing and waning pattern of consciousness, as seen in delirium. A subset of these patients may also develop catatonia.³ Non-convulsive status epilepticus (NCSE) is a heterogeneous disorder characterized by electrical seizures with minimal or no motor symptoms, and an altered mental status that may range from mild confusion to coma.⁵ NCSE is identified through electroencephalogram (EEG) findings and behavioral symptoms, as the motor signs are often subtle.⁵ Its clinical manifestations vary enormously and may include catatonia.⁷

We report a case of a patient with late-onset manic syndrome, followed by waxing and waning level of consciousness, and catatonic features. EEG findings were consistent with NCSE. The patient responded to immunotherapy, suggesting the probable diagnosis of autoimmune encephalitis (AE).

CASE REPORT

A 51-year-old Caucasian man, married, with no previous psychiatric illness, was transferred to Rhode Island Hospital (RIH) from another facility in early February 2017, due to a four-week history of psychomotor agitation and aggressive behavior. Medical history was significant for inflammatory bowel disease (IBD). His medications included acetylsalicylic acid and over-the-counter supplements. Patient was a former tobacco smoker (quit at age 26), with occasional marijuana use and moderate daily alcohol intake. He had lost three jobs over the past four years and had been living with his wife and two daughters. From his psychiatric history, admission interview and from collateral information

received from wife, patient did not have bipolar illness and his interpersonal problems were deemed to be from personality traits rather than to longstanding mental illness. Psychiatric history was significant for physical abuse from father during childhood.

In the ED, initial head computerized tomography (CT) demonstrated a small left parafalcine and bifrontal subdural hematoma (SDH), secondary to a traumatic brain injury that the patient had endured three months prior to his presentation to the hospital; given this context, he was started on oral levetiracetam 500mg twice a day for seizure prophylaxis, per ED/neurosurgical protocol even though there is no formal indication for such neurologically.

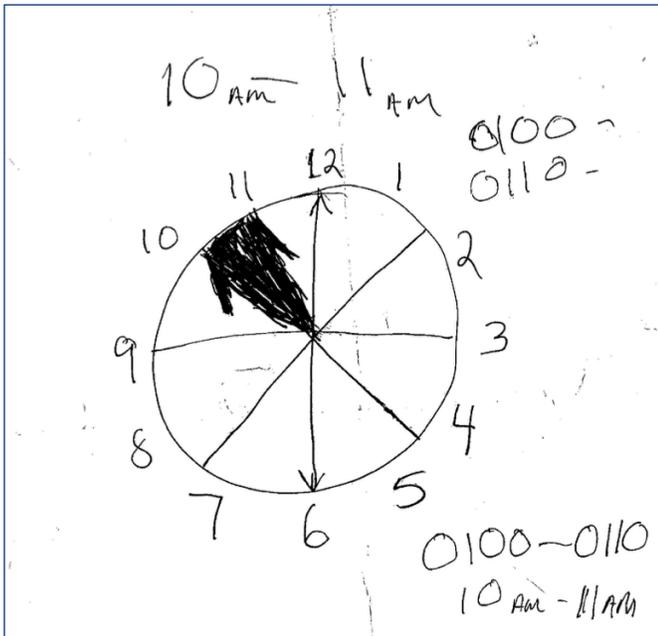
He later mounted a fever of 100.7F and was admitted to inpatient medicine for further evaluation of his fever and bizarre behavior. Initial infection workup, including Human Immunodeficiency Virus, Syphilis, Anaplasmosis and Lyme disease serologies were found negative. Given his acute encephalopathy, an EEG was done, which revealed occasional intrusions of slowing in the mid-temporal region, but no epileptiform activity was noted. CSF analysis revealed a glucose level of 60; protein, 49; and only 1 nucleated cell.

The fever resolved did not recur; his other vital signs remained normal. Further workup demonstrated a serum ammonia level of 84 mcg/dL, which then normalized on subsequent follow up (to 59 mcg/dL). Serum copper, zinc, urine porphyrins, serum thyroid, anti-TPO antibodies and liver function tests were also within normal limits. Serum sodium at that time was 129 mEq/L and urine osmolality >700 mOsm/kg, suggesting syndrome of inappropriate antidiuretic hormone secretion (SIADH) (the CT chest, abdomen, pelvis was only significant for large bowel obstruction, which was managed conservatively in parallel; no neoplasm identified to suggest a paraneoplastic source). Urinalysis was unremarkable and urine toxicology was positive for tetrahydrocannabinol only. Thiamine treatment was given in the setting of chronic alcohol use. Brain magnetic resonance imaging (MRI) was consistent with left juxtafalcine and small bifrontal SDH.

Given increased psychomotor agitation (yelling obscenities, impulsive behavior and pacing), paranoia and resolution of fever, the patient was transferred to inpatient psychiatry at day five of hospital admission.

Upon admission to the inpatient psychiatric unit, the

Figure 1. Patient's clock-drawing test (he was asked to draw "10 past 11")



patient was found alert, oriented and cooperative, maintaining good eye contact. He would occasionally present with an intense stare, pressured speech and constricted affect, alongside loose associations and racing thoughts. Insight and judgment were initially fair, then rated poor. He seemed overtly paranoid about his daughter as well as the nursing staff, but denied any hallucinations. No suicidal and homicidal thoughts or ideations were endorsed, either. Physical exam, including neurological and mini mental state examination (MMSE), were unremarkable. Clock-drawing test was significant for impaired executive function, perseveration, misplacements and over-inclusiveness (See **Figure 1**).

The initial psychiatric diagnosis was thought to be bipolar I disorder with acute manic episode and psychosis; he was started on olanzapine, which was titrated to 15mg daily. Due to minimal clinical improvement two days later, it was decided to switch olanzapine to oral risperidone 2mg twice a day. On the following days, daily oral lorazepam 1mg and valproate 1000mg were also prescribed; valproate was eventually switched to lithium due to worsening hyponatremia.

At day twelve of hospital admission, when shaving under supervision, the patient was found staring blankly. This episode was followed by a period of unresponsiveness, and subsequent similar staring spells. At day fourteen, he presented with prominent waxing and waning levels of consciousness, but no tonic-clonic movements were observed. Lithium toxicity was ruled out (serum level: 0.53 mmol/L). The case no more seemed to fit the provisional diagnosis of BD with psychosis; could DM or NCSE better explain it?

A prolonged EEG (off levetiracetam) was ordered, which showed generalized, monomorphic theta activity. The patient's behavior and altered mental status temporarily

improved after receiving lorazepam; the pattern of EEG also normalized, which, along with his initial clinical improvement, prompted a diagnosis of NCSE. The patient was transferred to neurology inpatient unit on the same day for further investigation.

A subsequent EEG revealed recurrent lengthy intrusions of generalized rhythmic activity, indicating subclinical seizures and a form of NCSE. His anti-epileptic drugs (AED) included daily oral levetiracetam 3g, lacosamide 400mg and valproate 1.5g. The patient no longer exhibited manic behavior, but he was continued on the same dose of lorazepam and risperidone. At day sixteen, the EEG demonstrated a buildup of rhythmic sharp activity over the left anterior quadrant, with concomitant video recording showing the patient with closed eyes, grimacing mildly and fidgeting with his hands. These seemed to cluster overnight and arise out of sleep. Two days later, another EEG revealed epileptiform discharge, which could have been either generalized in nature, or a rapidly spreading focal onset. Levetiracetam was then increased to 4g daily.

At day twenty-one, a new EEG revealed abundant runs of waxing and waning theta activity, which was relatively higher in amplitude and paroxysmal in nature, compared to his baseline. Topiramate 400mg was added to his AED and lacosamide was increased to daily 500mg. An additional CSF sample was collected, the results of which were unremarkable. A new head CT was significant for interval resolution of left parafalcine subdural hematoma.

A subsequent EEG, performed at day twenty-four of admission, did not show epileptiform transients; however, a greater degree of encephalopathy was noted this time. Phenytoin was added to his AED regimen.

On the following day, at day twenty-five, he presented with multiple episodes of unresponsiveness, dysarthria and significant palilalia. Interestingly, a tonic-clonic seizure was also recorded on the video EEG. The subsequent tracing showed significant rhythmic activity, particularly in the frontal regions, clinically evidenced as facial grimacing, with multiple instances of scratching his head and arms. Based on his prior manic episode with psychosis, which did not respond to psychiatric medication; abnormal motor activity, despite optimized antiepileptic treatment; and EEG findings compatible with encephalopathy, the presumptive diagnosis of autoimmune encephalitis came into consideration. With this in mind, the patient was empirically started on intravenous methylprednisolone 1g for five days and immunoglobulin, 5 doses. Notably, during this time, his brain MRI continued to demonstrate no abnormal findings, besides the SDH.

Whilst on the steroid and IVIG course, a repeat EEG was done. This EEG, from day twenty-eight, was described as numerous electrographic seizures arising from the bifrontal regions, occurring one to three times per hour on average, and lasting ten to thirty seconds at a time. Overall, these runs were relatively shorter and less "epileptogenic" in

appearance than the previous ones, validating immunologic involvement in the disease course.

On the last day of immunotherapy, the EEG was noted to display less frequent runs. The results of patient's CSF sample remained negative for inflammatory markers (anti-NR1, anti-LGI-1, anti-CASPR2, anti-Hu, NR1, GAD65, VGKC, Ma1 and Ma2, CV2 and amphiphysin). A serum panel was also sent but found inconclusive.

Ultimately, at day thirty-three of admission, the EEG showed findings indicative of mild diffuse encephalopathy, with suggested bifrontal epileptogenic regions, favoring left-sided predominance. However, no definite seizure activity was reported this time.

Upon hospital discharge, at day thirty-five of admission, the patient was found awake, alert, oriented to time, place, person and situation, following commands with no observed palilalia or dysarthria. He was overall pronounced stable from neurology and psychiatry standpoints. Patient's discharge medications included clonazepam, lacosamide, levetiracetam, phenytoin, topiramate, tamsulosin, thiamine, aspirin and sodium chloride tablets. One month after discharge, he was contacted by our team over the phone and reported feeling well, with return to his normal level of functioning. His wife was also able to confirm that patient was back to baseline.

DISCUSSION

Our case is worth sharing as it presents a diagnostic challenge due to considerable overlap in neuropsychiatric conditions and multiple confounding factors particular to our patient's presentation.

The diagnosis of bipolar disorder was proposed based on patient's initial presentation, given his manic episode with psychotic features. However, shortly thereafter, his level of consciousness started to fluctuate, raising the concern for delirious mania (delirious mania was considered the cause for his delirium as there was no acute precipitating physical illness recognizable at the time). As DM may be a life-threatening condition, early and assertive treatment is mandatory and predictive of better prognosis.² The team decided to initiate treatment of DM with a mood stabilizer and benzodiazepine.

Because of DM a prolonged EEG was performed, which revealed generalized, and monomorphic, theta activity. Following the empiric use of intravenous lorazepam, alongside a loading dose of levetiracetam, it was found that the patient's brain electrical activity had normalized, in addition to improving his behavioral and mental status. In view of this optimal clinical response, the main diagnostic hypothesis then became DM with non-convulsive status epilepticus.

As previously mentioned, post-ictal catatonia is related to NCSE and has variable presentation, such as alteration of consciousness and behavior, rigidity, mutism, catatonic

posturing and autonomic signs, even when there are no obvious convulsive seizures or a history of epilepsy.⁴ Our patient's patterns of EEG, his behavioral and mental status changes, including staring spells and unresponsiveness, as well as clinical and electroencephalographic improvement upon intravenous administration of lorazepam, all together supported this diagnosis.⁷

However, despite his initial clinical stabilization and EEG normalization, subsequent EEG tracings revealed an increasing degree of encephalopathy. This was followed by worsening of the clinical presentation, even when the patient was on an optimized treatment with AED, justifying a therapeutic test with immunotherapy. The test was successful. This corroborated the basis of an underlying organic immunological mechanism.

It is interesting to note that seizure activities in catatonia are reported to be about 16%, and an organic etiology is usually more common than psychiatric when the combination occurs.⁹ Therefore, from a teaching perspective, organic entities such as autoimmune encephalitis in catatonic states should be considered. As seizures and catatonia both respond to ECT and anticonvulsants, it is hypothesized that they may share a common pathogenesis; in fact, it is even suggested that catatonia may be the final common outcome pathway for abnormal brain seizure activity.¹⁰

His initial febrile presentation, in addition to agitation, bizarre and impulsive behavior, delusions, racing thoughts, oscillating level of consciousness and seizures (as observed in our patient), correspond to the clinical presentation of anti-NMDA receptor encephalitis, corroborating our hypothesis.⁷⁻⁹ An autoimmune process was postulated in the light of patient's clinical evolution, behavioral abnormalities and cognitive impairment, besides his abnormal electroencephalographic findings and response to immunotherapy. His autoimmune workup (both serum and CSF) remains negative to date, and although the identification of anti-NMDA receptor antibodies is required to confirm the diagnosis, false negative results can also be observed.¹⁰ Interestingly, antibodies are not detected in almost half of all autoimmune encephalitis cases.⁹

Finally, it remains unclear if the patient's underlying systemic inflammation, from IBD, and his concurrent SDH, could have played a role in his clinical presentation.

Our case illustrates challenges faced by clinicians seeking multidisciplinary approach to neuropsychiatric conditions and serves as a call to action for researchers and clinicians, helping them tailor their approach for patients who initially present with behavioral changes followed by (ictal) catatonia.

Acknowledgment

The authors gratefully acknowledge the patient profiled in this report for giving them permission to publish unidentifiable details about his case. We also thank the multidisciplinary team of inpatient psychiatry, C-L psychiatry and neurology at Rhode Island Hospital for their successful co-management in this interesting case. Dr. Camila Cosmo is supported by R25 MH101076.

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