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The Journal of *Medical Advancements and Research*

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Case Report

Agitation and Amnesia: A Case of Leptomeningitis of Unknown Origin

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CONFLICTS OF INTEREST STATEMENT

None of the above authors have any conflicts of interest to report regarding this case report.

ABSTRACT

Background: Leptomeningitis is a multifaceted condition with a plethora of underlying infectious and non-infectious etiologies. We present the clinical course and management outcomes of a case demonstrating atypical neuropsychiatric symptoms associated with steroid-responsive leptomeningitis of unknown etiology.
Case Presentation: A 41-year-old patient presented with a five-day history of intense mood lability, agitation, and amnesia without a discernable impetus or pattern. He exhibited no focal neurological deficits or signs on exam, nor did he exhibit symptoms consistent with a unifying DSM-V diagnosis. Non-contrast CT head was largely unremarkable. CSF studies revealed elevated total protein, elevated kappa free light chains, and lymphocytosis. MRI head notable for small nodular areas of leptomeningeal enhancement of the left parietal lobe. CT chest remarkable for old granulomatous infection with two tiny noncalcified nodules. Full body PET was solely remarkable for mild increased uptake involving segments of the bilateral common iliac veins. Comprehensive infectious and autoimmune workup was unfruitful. The patient's clinical syndrome was consistent with a diagnosis of leptomeningitis. High-dose corticosteroids were initiated and tapered, resulting in gradual subsequent resolution of the patient's neuropsychiatric symptoms.
Conclusions: While neuropsychiatric symptoms in isolation are quite a rare presentation for leptomeningitis, this case reiterates the importance of thorough clinical investigation prior to assigning a diagnosis encapsulated within the DSM-V.

Keywords: leptomeningitis, steroids, neuropsychiatric agitation

INTRODUCTION

Leptomeningitis is multifaceted condition with a vast array of presentations and underlying etiologies. From an imaging standpoint, foci of leptomeningeal enhancement are characteristic. While this finding in isolation is suggestive of leptomeningitis, it unfortunately aids minimally in narrowing the expansive differential diagnosis that accompanies this condition. This condition is known to be caused by a plethora of infectious, autoimmune/inflammatory, granulomatous, and paraneoplastic sources. With this case report, we present the clinical course and management outcomes of a case demonstrating atypical neuropsychiatric symptoms associated with steroid-responsive leptomeningitis of unknown etiology.

CASE PRESENTATION

A 41-year-old gentleman with a history of childhood traumatic brain injury and possible chronic traumatic encephalopathy in the setting of a prior long-term NFL career presented to the emergency department in the setting of a five-day history of “a complete breakdown.” This was further characterized as intense mood lability, namely unpredictable episodes of extreme rage, non-sensical tearfulness, and incapacitating anxiety without any discernible pattern or reproducible trigger. Prior to presentation to our medical center, the patient presented to an outside hospital for evaluation of these behaviors. Work-up, including laboratory studies and CT of the head, was negative for any acute process or pervasive inciting factor.

Upon physical examination, the patient was afebrile and hemodynamically stable. Neurological examination was without a localizing deficit. Mental status exam was notable for intense eye contact, behaviors ranging from calm to intermittently explosive and frustrated as well as deficits in short term memory. Laboratory studies, including CBC, CMP, and blood glucose were within normal limits. Psychiatry consultation was obtained, at which time it was recommended that neurology involvement be pursued.

Regarding imaging, CT of the head revealed nonspecific encephalomalacia and chronic ischemic changes. MRI of the head revealed small nodular areas of leptomeningeal enhancement in the left parietal and possibly right parietal lobe with a small focus of cortical FLAIR hyperintensity. Empiric meningitis coverage was initiated, and inpatient admission was sought for further workup.

CSF examination revealed elevated white blood cell count with 97% lymphocytes, elevated total protein, and elevated kappa free light chains. Infectious workup was negative, and empiric meningitis coverage was discontinued at the urging of the infectious disease consultant.

Upon further chart review and obtaining outside records, it was discovered that the patient had a few indeterminate pulmonary nodules in October 2016 which were lost to follow up. Given these historical lesions and the patient’s presenting leptomeningeal enhancement, CT of the chest and PET were obtained to rule out sarcoidosis. CT of the

chest was without evidence of thoracic involvement by sarcoidosis, solely revealing a historical, resolved granulomatous infection with two residual, tiny noncalcified nodules. PET was notable for mild increased uptake involving segments of the bilateral common iliac veins. There was no evidence of a hypermetabolic neoplastic process.

With the initial workup complete, providers expressed confidence that an infectious etiology for the patient's leptomeningitis was far less likely than an autoimmune, inflammatory (primary angiitis?), or paraneoplastic origin. Therefore, high dose IV steroids with a subsequent, prolonged oral steroid taper was initiated. He was discharged with follow up in the outpatient setting.

On this steroid regimen, the patient displayed initial improvement of his neuropsychiatric symptoms, namely his behavioral outbursts and mood lability. He continued to follow with psychiatry and neurology in the outpatient setting. The following additional workup was obtained and largely unremarkable: MRA of the head, MRV of the head, EEG, CTA of the chest/Abdomen/Pelvis, Carotid Ultrasound, and extensive autoimmune workup (initiated with admission, yet resulted over a matter of weeks). As the steroid taper concluded, agitation returned. Thus, long term immunosuppression with mycophenolate mofetil was pursued. Given intractable headaches, the patient was only able to tolerate this medication for a short time. Given the relapsing/remitting nature of his disease without a clear underlying etiology, continued immunosuppression, meningeal biopsy, and rheumatology referral were encouraged. The patient elected to be monitored off immunosuppression in the interim to rheumatology input and discussion of meningeal biopsy with neurosurgery. Unfortunately, the patient was lost to follow up.

DISCUSSION

This 41-year-old gentleman presented with behavioral disturbance and a negative initial workup. Key positive findings include elevated white blood cell count with 97% lymphocytes, elevated total protein, and elevated kappa free light chains on CSF studies, in addition to leptomeningeal enhancement on MRI. Despite extensive, multifaceted workup exploring a vast differential, a clear underlying etiology has yet to be identified. Through extensive literature review, it appears that the better-known causes of leptomeningitis include several infectious etiologies (viral, tuberculosis, and syphilis), in addition to metastatic neoplasms and rheumatologic conditions (namely rheumatoid arthritis, primary angiitis of the CNS, and sarcoidosis). While neuropsychiatric symptoms in isolation are quite a rare presentation for leptomeningitis, this case reiterates the importance of thorough clinical investigation prior to assigning a diagnosis encapsulated within the DSM-V.

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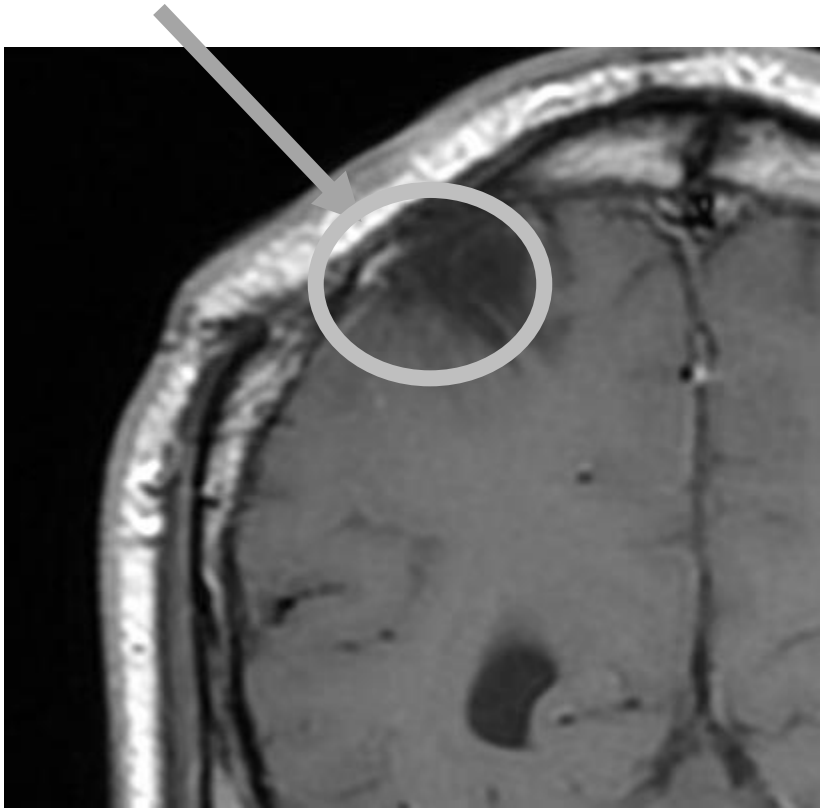
FIGURES AND TABLES

1) Patient's MRI of the brain demonstrating Leptomeningeal enhancement



Case Report

A Case of Malignant Catatonia with Fragile X Syndrome

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CONFLICTS OF INTEREST STATEMENT

None of the above authors have any conflicts of interest to report regarding this case report.

ABSTRACT

This case examines an example of the intricacies of comorbid intellectual disability and catatonia. The patient was previously a high-functioning, active adult with a full-time job and involvement in multiple sporting activities. Likely due to psychosocial stressors caused by the COVID-19 pandemic, the patient developed depressive and anxiety symptoms with catatonic features. After minimal improvement with benzodiazepines, a course of electroconvulsive therapy (ECT) was performed, complicated by malignant catatonia and urosepsis. Multidisciplinary cooperation allowed for bedside ECT treatments alongside ICU-level care for patient recovery. Prior studies suggest the possibility of genetic and physiologic predispositions for resistance to benzodiazepines associated with intellectual disability and autism; however, these are inconclusive and require further exploration. Malignant catatonia shares many clinical features with other life-threatening conditions; therefore, prompt treatment of medical comorbidities and psychiatric treatment of catatonia with ECT is crucial and may require cross-functional team efforts.

Keywords: Fragile X Syndrome, Catatonia, Malignant Catatonia, Electroconvulsive Therapy

INTRODUCTION

Fragile X syndrome is one of the most common genetic causes of intellectual disability. As a X-linked dominant disorder, it is most often caused by an expanded trinucleotide (CGG) repeat, resulting in loss of function of the FMR1 gene at Xq27.3. CGG expansions of >200 repeats result in full mutation and the classical phenotype in both males and females which includes elongated face with prognathism, large ears, and testicular enlargement (following puberty) or primary ovarian insufficiency [1]. It is estimated that up to nearly 67% of males with Fragile X syndrome meet criteria for autism spectrum

disorder (ASD) and may have greater impairments in cognitive skills, language, social interaction, and adaptation [2]. They may also have avoidant behaviors, stereotypy, anxiety symptoms, aggressive behavior, inattention/overactivity, and mood instability.

Catatonia is a behavioral symptom most commonly associated with psychotic, neurodevelopmental, and mood disorders. It is characterized by three or more of the following symptoms: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerisms, stereotypy, unprovoked agitation, grimacing, echolalia, or echopraxia. The severity of these symptoms is generally scored by using the Bush-Francis Catatonia Rating Scale, a 23-item standardized scale that has become the generally accepted standard [3]. The scale consists of 17 items rated on a scale of 0 to 3, with the first 14 of those 17 items as a screening tool for symptoms the first 24 hours of monitoring. A score of 2 or more indicates likelihood for catatonia and recommendation for a full rating, with the last 6 items rated “0 (absent)” or “3 (present)” and a maximum score of 69 [4]. First line treatments for catatonia include benzodiazepines, commonly known as “Ativan challenge” and/or electroconvulsive therapy (ECT). In the case of malignant catatonia, which is characterized with fever, autonomic instability, delirium, and rigidity, ECT is the definitive treatment for symptoms [5].

CASE

Mr. A is a 48-year-old Caucasian male who first presented to the psychiatric clinic in October 2021, for chief complaint of depression and anxiety. At the time of intake, he was primarily non-verbal, with most of the history provided by his mother and legal guardian. The patient’s mother reported at intake that the patient had recently lost his restaurant job of 5 years following bizarre changes in behavior (e.g., cleaning dishware on the floor, walking off restaurant property). His mother reported a change in behavior approximately 6 months prior (March/April 2021) and noted significant functional decline throughout COVID-19 pandemic. The patient was previously high functioning and very active in the local Special Olympics chapter, where he participated in multiple sporting activities. At the intake appointment, the patient was observed to also display catatonic features, including posturing, echolalia, purposeless movement, and negativism (also known as gegenhalten) with a Bush-Francis catatonia score of 21. He was noted to have decreased appetite with a weight loss of over 30 pounds over the previous 6 months.

The patient had previously been treated for his symptoms with sertraline 25-50 mg daily for depression and anxiety. At the time of intake appointment, sertraline was discontinued and mirtazapine 15 mg at bedtime daily was started for appetite enhancement profile. Diazepam 5 mg twice daily was initiated for catatonic symptoms. Over the next 3 months, diazepam was titrated up to 7.5 mg three times daily, then switched to lorazepam 1 mg three times daily due to sedation from diazepam for catatonia. Mirtazapine was titrated up to 45 mg at bedtime daily to target anxiety and depressive symptoms. At patient’s follow-up visit in May 2022, he was observed to have minimal improvement in his catatonia and depressive symptoms compared to intake. Mirtazapine was further increased to 60 mg at bedtime daily, and ECT was strongly recommended; however,

patient's guardians did not feel he was ready to be admitted to the hospital or complete ECT. A trial of lorazepam 1 mg four times daily was introduced in July 2022; however, the patient's mother reported patient appeared too sedated and stuporous with increased frequency of dosing. The patient's guardians (mother and father) agreed to trial of ECT; however, due to Kansas State Law, a court-ordered amended guardianship, obtained in late July 2022, was required prior to treatment. Prior to initiation of treatment, patient's laboratory results indicated evidence of an asymptomatic urinary tract infection (urinalysis positive for nitrites, leukocyte esterase, and moderate bacteria), and a five-day course of nitrofurantoin (100 mg twice daily) was prescribed for treatment.

Mr. A started his initial course of ECT in late August 2022, with right unilateral positioning and had notable improvement in affect after his third session. Following the patient's fifth session, his mother noticed that patient became remarkably less expressive. The patient missed his next session due to illness presented to urgent care in early September 2022, and was evaluated for urinary tract infection (UTI) and COVID-19 infection. The patient's point-of-care urinalysis at urgent care did not report any criteria for a UTI; however, a subsequent urine culture of the same specimen grew >100,000 CFUs of Escherichia coli. He resumed his initial course of ECT with seventh session. At this session, he was noted to have worsening signs of catatonia and switched to a bilateral procedure. Due to concerns of more side effects following switch to bilateral ECT including his family reporting he was having increased mutism, ECT was subsequently switched back to right unilateral procedure at eighth and ninth session.

The patient was scheduled to undergo his tenth ECT session; however, he presented to the emergency department with fatigue and lethargy, altered mental status, extreme stiffness, minimal responsiveness, and a fever of 102.9F. Patient was subsequently admitted to the medical floor and noted to have blood and urine cultures positive for E. coli. Within the same day, the patient became increasingly febrile with maximum reported temperature of 106F and was transferred to medical intensive care unit (ICU). Laboratory studies on transfer were notable for a climbing creatine kinase 596 to 1293 in 24 hours. During ICU admission, the patient was treated with fluid resuscitation and IV piperacillin-tazobactam. Antibiotics were subsequently stepped down to IV ceftriaxone following culture and sensitivity. Patient's vital signs continued to destabilize, and his airway became increasingly compromised with medical treatment of sepsis. Malignant catatonia was suspected with a trigger being sepsis, as well as contributions from missed home doses of lorazepam and interruption in ECT sessions. With clearance from cardiology and neurology services, patient's ECT course was resumed with bedside procedure for two additional sessions. Patient's fever subsided after first bedside ECT treatment with rapid change in mental status and activity following second bedside session. Following medical stability and discharge, the patient was transferred to inpatient rehabilitation and completed four additional ECT treatments for a total of 15 sessions. With resumption of ECT, he became more verbally active and engaged with providers and family. His functional status quickly improved to a baseline prior to hospitalization.

Patient was seen for outpatient follow-up approximately 1 month after hospital admission. It was noted the patient had missed further scheduled ECT sessions and was recommended to continue ECT on a bi-weekly basis. He completed a total of 17 ECT sessions as of his follow-up visit in early January 2023, during which time his co-guardians made the decision to halt further ECT treatments.

DISCUSSION

For patients with major depressive disorder, selective serotonin reuptake inhibitors (SSRIs) are typically used as the first line agents for treatment. This patient had been prescribed sertraline up to 50 mg prior to establishing care with the clinic. Though this dose was likely subtherapeutic, the patient's severe weight loss and lack of appetite were of primary concern, and the decision to trial mirtazapine, given a more favorable profile for appetite enhancement and weight gain, was made. Some studies have suggested that mirtazapine may have an earlier effect than most SSRIs [6]. As patient met criteria for generalized anxiety disorder, which may have been better explained by catatonia or anxious distress with depression, mirtazapine was titrated to a maximum dose of 45 mg and above FDA-approved dosing to 60 mg with benefit.

Recent studies have indicated interest in the comorbidity of catatonia with ASD and is increasingly recognized at a rate of 4%-17% in adolescents and adults with ASD [7]. Common overlapping symptoms include social indifference, echolalia, and repetitive mannerisms can create difficulties in differentiating one diagnosis from the other, as patients with Fragile X Syndrome may have comorbid ADHD or mood disorders as well. Shorter and Wachtel hypothesize that the "iron triangle" of mixed ASD, psychosis, and catatonia may be presentations of the same underlying brain disorder [8].

There have been several proposed explanations for the link between catatonia and ASD, including abnormal GABAergic functioning, cerebellar structures, and genetic linkage via chromosome 15. As catatonia is associated with mood disorders, patients with ASD have been shown to be more susceptible to mood and anxiety disorders and therefore more susceptible to catatonia [9]. In this case, abnormal GABAergic functioning resulting in an imbalance in excitatory and inhibitory neuronal circuits. This may explain the patient's poor response to benzodiazepines for catatonia and notable improvement with ECT. This theory has been demonstrated in another male patient with Fragile X Syndrome [10,11].

The low incidence of malignant catatonia and its similarity in presentation to other life-threatening medical emergencies, particularly sepsis and neuroleptic malignant syndrome (NMS), may make the diagnosis difficult. Previous case reports have examined instances of malignant catatonia in the presence of infection and without, as well as with and without the use of antipsychotics. Recommended treatment includes prompt administration of benzodiazepines within 24 hours and concurrent ICU-level medical care of potential complications (e.g. hemodynamic instability, poor airway clearance, electrolyte imbalances, and thromboembolic disease) coordinated with psychiatric care for

sedation and ECT treatments [12]. ECT may the definitive treatment for malignant catatonia should benzodiazepines be ineffective [13].

CONCLUSION

This case illustrates the complexity of managing both psychiatric and medical conditions in patients with intellectual disability and/or ASD. While there are many overlapping symptoms of Fragile X associated intellectual disability and symptoms of catatonia, it is important to understand and analyze changes in behavior from patient's established baseline [14]. When the patient cannot verbalize this, collateral information from parents/guardians is critical, particularly video of behaviors. Common maladies that are easily treated, such as urinary tract infections, may not appear symptomatic to patients with language deficits and can easily escalate to more severe illnesses without frequent observation and attention to treatment compliance. It is important for providers to understand communication gaps among fellow providers, the patient, and guardians. This case also provides a remarkable example of multi-disciplinary efforts to provide urgent treatment of ECT, demonstrating flexibility across a health system.

Following all elective ECT sessions, at follow-up in early January 2023, the patient's Bush-Francis Catatonia Rating Scale reduced to a score of 4. The patient continued to display notable mutism; however, he had a greater range of expressive affect and was able to respond to questions appropriately. The patient's guardians reported overall improvement in physical activity with continued apathy and lethargy. Mr. A's guardians did not express a desire to resume ECT, and a trial of methylphenidate 5 mg twice daily was started for depression augmentation and daytime fatigue. Methylphenidate was discontinued due to reported agitation and a trial of clonazepam, as an alternative for lorazepam, for catatonia resulted in a paradoxical reaction of increased depressive symptoms and agitation. At the patient's final follow-up in June 2023, patient had been resumed on lorazepam 1 mg three times daily with additional 0.5 mg as needed for insomnia. The patient was able to sporadically answer questions with more expansive affect and no notable posturing.

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Case Report

Fluvoxamine-induced Mania in an Elderly Patient Treated for COVID-19

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CONFLICTS OF INTEREST STATEMENT

None of the above authors have any conflicts of interest to report regarding this case report.

ABSTRACT

The COVID-19 infection treatment response resulted in multiple agents adapted to be used off-label in an effort to lessen the severity of symptom burden. This included the use of fluvoxamine in addition to other agents. This case report serves as a reminder of potential adverse effects that can occur without warning or history of similar presentation when using psychotropic agents. Fluvoxamine use contributed to this patient's presentation of mania and resulted in hospitalization as well as clinical impairment in function.

Keywords: COVID-19, Fluvoxamine, drug-induced mania

INTRODUCTION

New episodes of mania have been reported in association with the coronavirus disease 2019 (COVID-19) [1]; however, more research is needed to determine whether these findings are causally related to infection with the SARS-CoV-2 virus, are better explained by medications used to treat COVID-19 (e.g., corticosteroids), or reflect an inciting event resulting in initial presentation of bipolar disorder. Further complicating this picture, fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), has been trialed in recent months as an experimental therapy for COVID-19 on the grounds of having the potential to reduce cytokine production as a sigma-1 receptor agonist [2]. In this case, we present a patient with no significant psychiatric history who exhibited new-onset mania following treatment with fluvoxamine for a positive COVID-19 test.

CASE REPORT

“Mr. X” is a 75-year-old gentleman with a history of remote alcohol use disorder in sustained remission and no other psychiatric history who presented to the emergency department with three weeks of poor sleep, pressured speech, expansive mood, grandiose delusions, and tangential thought. The patient’s wife, a healthcare worker who had known the patient for over 35 years, confirmed that her husband had never exhibited symptoms like these before.

Forty days prior to presentation, the patient tested positive for COVID-19. He called his primary care physician who prescribed a 17-day course of fluvoxamine (100 mg twice daily x 2 days, followed by 100 mg daily x 15 days). During this time, the patient never developed an oxygen requirement and thus never received treatment with corticosteroids; nor did he take any other medications apart from alprazolam (0.25 mg nightly), which had been prescribed by his primary care physician for sleep initiation. Approximately five days after completing the course of fluvoxamine, the patient’s manic symptoms became apparent and gradually worsened over the next two weeks until his wife convinced him to present to the emergency room.

Laboratory evaluation was significant for a mild normocytic anemia (hemoglobin 12.9, mean corpuscular volume 95.5), blood glucose 131 and mildly elevated creatine kinase of 458. Collateral from the patient’s wife revealed that he had been eating and drinking very little during the preceding weeks. His BMI on presentation was 21.7 kg/m^2. Additional laboratory studies included a negative blood alcohol level, negative salicylate and acetaminophen level, negative serum troponin, unremarkable urinalysis, and unremarkable urine drug screen. Additional work up included: TSH, anti-thyroperoxidase antibodies, anti-thyroglubulin antibodies, vitamin B12, ESR, CRP, and heavy metal screens (lead, arsenic, mercury, cadmium) were within normal limits. Syphilis antibody, HIV screen, rheumatoid factor, and SARS-CoV-2 polymerase chain reaction were negative on the day of admission.

Imaging studies consisted of CT of the head without contrast, MRI of the brain with and without contrast, and MRA of the head. These studies were unremarkable, revealing mild supratentorial white matter disease consistent with chronic microvascular ischemic changes and no flow limiting stenoses or evidence of inflammation. Additional studies included a routine EEG which revealed no epileptiform discharges or lateralizing signs.

The patient was admitted with the provisional diagnosis of medication-induced mania. Given his age, his decreased appetite, the brevity of the expected course of treatment, and the treating team’s desire to promote sleep while avoiding the use benzodiazepines, he was started on olanzapine 5 mg nightly. This was gradually increased to 10 mg twice daily, during which time the patient experienced gradual improvement in manic symptoms until his discharge home 14 days following admission.

DISCUSSION

The patient's age and minimal psychiatric history prior to admission made a new diagnosis of a primary psychiatric disorder such as bipolar disorder or schizoaffective disorder implausible. Although reports of older individuals with a history of primary mood disorder have been noted to exhibit new-onset mania in the context of COVID-19 infection have surfaced, and fluvoxamine has been associated with mania as have other SSRIs [3], this is—to our knowledge—the first reported case of medication-induced mania following experimental treatment of COVID-19 with an SSRI.

This case highlights the need for caution and vigilance when prescribing SSRI's, particularly when such medications are prescribed (1) at high doses, (2) for older patients, and (3) in patients with no known antidepressant trials who have minimal psychiatric history. It is also important to consider the adverse effects of medications when prescribing them for off-label use. All of these circumstances coalesced in the case of Mr. X.

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Case Report

Pre-emptive Blood Monitoring to Detect Early Signs of Clozapine-induced Myocarditis: A Case Report

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CONFLICTS OF INTEREST STATEMENT

None of the above authors have any conflicts of interest to report regarding this case report.

ABSTRACT

A 22-year-old male and a 29-year-old male were initiated on clozapine for treatment resistant schizophrenia. Each had failed multiple prior antipsychotic medication trials. Both patients developed myocarditis, a rare but likely underreported side effect of Clozapine pharmacotherapy, within the first 4 weeks of treatment. Our 29-year-old patient was followed on a pre-emptive blood monitoring schedule, which included weekly CRP and Troponin lab values, upon medication initiation. This monitoring resulted in earlier detection of myocarditis and thus resulted in preserved cardiac function on echocardiogram. We suggest that this enhanced blood monitoring schedule in addition to the required complete blood count monitoring should be considered by practitioners initiating clozapine pharmacotherapy to identify early signs of this challenging diagnosis.

Keywords: clozapine, myocarditis, Schizophrenia, REMS, medication monitoring

INTRODUCTION

Treatment resistant schizophrenia is defined as non-response to adequate trials of two antipsychotic agents without clinically significant reduction in symptoms as well as persistent impairment in global functioning[1]. Clozapine is the only antipsychotic medication with an FDA indication for treatment resistant schizophrenia[2]. It is often considered as a last line agent by clinicians due to its side effect profile and requirements for frequent lab monitoring. Strict blood monitoring, as well as a slow dose titration to therapeutic levels, can reduce potentially lethal adverse drug reactions including myocarditis. This

case report describes two patients in our clinic who developed clozapine-induced myocarditis. After the first case, our clinic changed the monitoring policy for clozapine initiation in an effort to reduce future harm. After this change, we were able to rapidly detect cardiac issues and, thus, demonstrated the benefits of pre-emptive blood monitoring in early recognition of this potentially lethal adverse medication effect.

CASE 1:

JN is a 22-year-old white male with refractory schizoaffective disorder admitted for his sixth psychiatric admission within a calendar year for worsening psychosis evidenced by delusions, paranoia, and erratic behavior. He had multiple failed antipsychotic trials due to inefficacy and was also particularly sensitive to antipsychotic medication side effects including dystonia and orthostasis. Due to multiple failed medication trials, risperidone 4 mg at bedtime was switched, with a cross titration, to clozapine 300 mg at bedtime. He initially complained of sedation, sialorrhea, increased thirst, and indigestion. He complained of chest discomfort that was presumed to be secondary to indigestion as it was relieved with an antacid. He also complained of feeling dizzy upon standing with an increased heart rate to 120 beats per minute (bpm), but vitals were otherwise normal. He attributed his dizziness to being on three medications simultaneously and felt better once the titration was completed. At his outpatient follow up appointment five days post discharge and nineteen days after Clozapine initiation, he presented with a heart rate of 131 bpm and complained of a flu-like illness which raised concern for myocarditis. A C-reactive protein (CRP) and troponin were obtained which revealed a CRP of 180.9 mg/L and troponin of 0.22 ng/mL. An EKG was obtained which showed sinus tachycardia (heart rate 120 bpm) with no T wave changes. He was subsequently instructed to present to the emergency department (ED) for evaluation and admitted to the hospital for suspected myocarditis (Figure 1). Echocardiogram revealed diffuse, severe left ventricular (LV) dysfunction with EF 25%. Cardiac MRI also demonstrated moderate to severe right ventricle (RV) dysfunction in addition to mild patchy increased signal intensity within the LV apex and posterior papillary. Testing for alternative etiologies was negative. Clozapine was discontinued and evidence-based therapies started for heart failure. Cardiac function returned to normal over the course of several months.

CASE 2:

CK is a 29-year-old white male with diagnoses of schizophrenia and obsessive-compulsive disorder. He was seen for an intake appointment in our outpatient clinic and was being prescribed ziprasidone 80 mg twice daily and fluphenazine decanoate 50 mg every 2 weeks with additional oral fluphenazine supplementation of 5 mg daily and 10 mg prior to bedtime. He had a history of treatment failures or side effects on multiple other antipsychotic agents. Chief psychiatric symptoms were paranoia about being monitored by electronic devices and negative symptoms including flat affect and social withdrawal. He was followed in our clinic for about 8 weeks on this antipsychotic regimen and did complete 12 treatments of electroconvulsive therapy to help with depressed mood. His psychotic symptoms remained debilitating following these treatments, and the decision was made to initiate a clozapine titration schedule with a goal

dose of 150 mg daily and to taper other antipsychotic agents to discontinuation. Patient was also referred to our clinical pharmacist who monitored for adverse effects in collaboration with the physician. Strict blood monitoring in compliance with clozapine Risk Evaluation and Mitigation Strategies (REMS) and weekly CRP and troponin levels drawn at the beginning of the titration were monitored. CRP increased to 46.8 mg/L in week 4 of titration when patient had reached titration goal of 150 mg daily. He was also tachycardic with heart rate of 114 bpm. He did not complain of cardiac symptoms but did have a non-productive cough. Repeat testing three days later showed increasing CRP of 70 mg/L and Troponin of 0.07 ng/mL. Patient was sent to the ED and subsequently admitted due to concern for clozapine-induced myocarditis (Figure 2). Clozapine was not continued upon admission and he was not rechallenged. Repeat troponins trended downward while CRP continued to increase with a peak of 140.78 mg/L on hospital day 3. Echocardiogram revealed mild LV dysfunction with EF of 55%. Cardiac MRI did not show any gadolinium enhancement to suggest ischemic, focal inflammatory, or diffuse infiltrative process. The psychiatry consult service saw the patient on hospital day 2 and recommended starting oral fluphenazine 10 mg daily upon discharge. Patient was discharged on hospital day 4 after CRP decreased with no significant cardiac impairment.

DISCUSSION

These two contrasting cases demonstrate the importance of obtaining weekly CRP and troponin levels, in addition to CBCs with differential, during the first four weeks of clozapine titration. Clozapine is recognized as clinically superior to other antipsychotic medications in patients with schizophrenia who have been designated as treatment resistant as well as those patients without this designation[3]. Although this medication has shown greater efficacy in a head-to-head trial toward improvement in psychotic symptoms, clinicians often find themselves to be hesitant in initiating this medication due to adverse medication reactions such as myocarditis[4]. Diagnosing clozapine-induced myocarditis can be challenging as patients may present as asymptomatic or with non-specific symptoms. The gold standard for diagnosis is myocardial biopsy, but this is used infrequently and is not always feasible for patients being followed in the outpatient mental health setting[5]. Also, about 25% of patients started on clozapine experience tachycardia, possibly due to the medication's direct vagolytic effects, which can further confound this diagnosis[5]. There is a lack of specific monitoring guidelines for myocarditis[6]. All these variables explain the wide-ranging prevalence between 0.03% to 3% in our literature review with significant underreporting likely lowering these values [7 8]. Clozapine-induced myocarditis was found to be fatal in 21% of the 85 cases in which outcomes were able to be reported[9].

In one study, 83% of clozapine-induced myocarditis occurred between day 14-21 of titration[10]. Combining a troponin (> 2 times upper limit of normal) and CRP (> 100 mg/L) gave 100% sensitivity in symptomatic cases although the sensitivity in asymptomatic cases was unknown[10]. Monitoring as suggested by this study was implemented in our outpatient clinic by the pharmacist after J.N's case. This monitoring protocol, in addition to checking vitals and asking about clinical symptoms, appears to be reasonable in

preserving heart function. We believe that pre-emptive monitoring allowed us to recognize signs of myocarditis earlier in the disease progression for C.K. which resulted in preserved ejection fraction on echocardiogram and no signs of destructive process on cardiac MRI as compared to the imaging studies for J.N.

CONCLUSION

Clozapine can be a life-changing medication for individuals with treatment resistant schizophrenia. However, it is important to have a high suspicion for potentially lethal adverse drug reactions including myocarditis. The prevalence of myocarditis is thought to be underreported in current literature due to heterogeneity in patient presentation and lack of standardized lab monitoring protocols. Adding cardiac and inflammatory markers of CRP and troponin monitoring to the required CBC with differential for at least the first four weeks of clozapine titration is helpful for identifying early signs of clozapine-induced myocarditis during its peak incidence and preserving cardiac functioning as evident by the disease progression in these two cases.

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ADDITIONAL FIGURES

Day 1	Day 4	Day 5	Day 8	Day 15	Day 17	Day 23
Clozapine initiation	ANC ↓ 50% from baseline	HR 120	ANC ↑ to baseline	Clozapine stopped ESR 36 CRP 18.9 Trop 0.22 Clozapine total level = 1,254 Diffuse hypo-kinesis, EF ~30%	Temp = 103.1° F HR ≥ 120	Normal LV and RV size and function, EF 55%

Figure 1: J.N. Timeline

Day 1	Day 2	Day 9	Day 16	Day 23	Day 26	Day 27	Day 29	Day 30
Clozapine Initiation	Baseline CRP 2.90 mg/L, Troponin negative	CRP 4.60 mg/L, Troponin negative	CRP 3.40 mg/L, Troponin negative	CRP increased to 46.80 mg/L, Troponin negative, HR 112-114	CRP increased to 70.0 mg/L, Troponin 0.07 ng/mL, EKG with borderline T wave abnormalities **-Patient hospitalized**	Echo: no segmental wall motion abnormalities, 55% EF	CRP peak at 140.78 mg/L, Troponin returns to negative	Cardiac MRI: EF 53%, normal ventricle size, no valve abnormalities, normal systolic function

Figure 2: C.K. Timeline

Case Report

Safe and Efficacious Utilization of Rocuronium During Electroconvulsive Therapy in Cases of Historical Succinylcholine-associated Anaphylaxis: A Case Report

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CONFLICTS OF INTEREST STATEMENT

None of the above authors have any conflicts of interest to report regarding this case report.

ABSTRACT

Rocuronium is a notorious culprit for anaphylaxis and anaphylactoid reactions during anesthesia induction. We present a case of safe and efficacious utilization of multiple administrations of rocuronium-sugammadex in a 47-year-old male with a personal history of succinylcholine-mediated anaphylaxis and a family history of malignant hyperthermia undergoing a course of electroconvulsive therapy (ECT) for the management of depressive symptoms. A treatment series totaling eight sessions of electroconvulsive therapy was completed and rocuronium-sugammadex was tolerated without evidence of hypersensitivity. Despite its historical proclivity for adverse reactions, rocuronium is a safe and effective paralytic agent to utilize in patients in which succinylcholine is contraindicated, either due to anaphylaxis concerns or a family history of malignant hyperthermia.

Keywords: Rocuronium, Sugammadex, Succinylcholine-mediated anaphylaxis, electroconvulsive therapy

INTRODUCTION

Rocuronium is a rapid-onset, intermediate-duration, non-depolarizing neuromuscular blocking agent that works via competitive acetylcholine receptor antagonism at the neuromuscular (Nm) nicotinic receptors, resulting in the prevention of consequent motor endplate action potentials.[1,2] Given these attributes, in addition to the advent and ease of use of the novel gamma-cyclodextrin molecule reversal agent Sugammadex,

Rocuronium and other non-depolarizing neuromuscular blocking drugs have proven to be highly useful in patients who otherwise have a contraindication to the use of the more traditionally utilized depolarizing neuromuscular blocker succinylcholine. Despite the alternative viability of non-depolarizing agents for paralysis during ECT procedures, epidemiological studies from several countries (Norway, Australia, New Zealand, Spain, and South Korea, to name a few) reveal varied data regarding the risk of perioperative hypersensitivity reactions with succinylcholine versus rocuronium and other non-depolarizing agents. These studies reveal that the risk of anaphylaxis and anaphylactoid reactions with rocuronium is anywhere from comparable to even greater than that of succinylcholine.[3,4] Furthermore, when comparing the rates of cross-reactivity between succinylcholine and non-depolarizing neuromuscular blocking agents, patients with prior succinylcholine anaphylaxis cross-reacted most often with rocuronium. [4] Despite its association with anaphylaxis, cross-reactivity, and anaphylactoid reactions, this case report demonstrates the safe and efficacious use of rocuronium for muscle paralysis during the ECT series in an individual with a personal history of succinylcholine-mediated anaphylaxis and a family history of malignant hyperthermia.

CASE REPORT

A 47-year-old, 83-kilogram male with a history of schizoaffective disorder bipolar type, posttraumatic stress disorder, succinylcholine-associated anaphylaxis, and a family history of malignant hyperthermia in a first-degree relative (mother) was referred for ECT for persistent, treatment-refractory depressive symptoms. Prior medication trials included three SSRIs/SNRIs, three mood stabilizers, and three atypical antipsychotics. Current scheduled medication regimen included chlorpromazine and sertraline. Given the patient's provided and demonstrated histories of adverse reactions to paralytics, namely in respect to succinylcholine, the combination of rocuronium-sugammadex was trialed as an alternative paralytic regimen. An initial rocuronium dose of 30 mg was selected and, post-procedurally, reversed with Sugammadex 180 mg. The anesthetic induction agent utilized for all treatments was methohexital. Quantitative monitoring of rocuronium effect with train-of-four (TOF) count via acceleromyography (AMG) was utilized with each ECT procedure. By virtue of this monitoring and patient response, in addition to psychiatrist and anesthesiologist expertise, rocuronium was titrated to 40 mg—with subsequent reversal using Sugammadex 200 mg—for treatment numbers seven and eight. A treatment series totaling eight ECT sessions was completed, with the patient reporting overall improvement in his depressive symptoms. The combination of rocuronium-sugammadex was tolerated without clinical signs or symptoms of hypersensitivity, anaphylaxis, or anaphylactoid reactions.

DISCUSSION

With studies revealing that the risk of anaphylaxis, anaphylactoid reactions, and cross-reactivity between rocuronium and succinylcholine is overall greater with rocuronium, a heterogeneity of factors, including pre-sensitization (in addition to region, for varied use of rocuronium by region may lead to more potential pre-sensitization), genetic predisposition, life history, comorbid conditions, and pathophysiological factors contribute to the development of hypersensitivity.[5] Thus, one is unable to say with certainty why the

above-described patient did not exhibit a hypersensitivity reaction, while numerous others, per review of the literature, had a much more tenuous course with the use of rocuronium.[3] Given the nature of this case report, this observation is merely a snapshot into a sole patient case. Other considerations that must be taken into account prior to use of the combination of rocuronium-sugammadex include anesthesiologist and psychiatrist expertise, in addition to upholding concern for cost-effective care (given the relatively high expense of sugammadex). In summary, the combination of rocuronium-sugammadex may be an efficacious, well-tolerated paralytic and reversal agent in individuals with a personal history of succinylcholine-mediated anaphylaxis and/or a family history of malignant hyperthermia.

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