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Case Report

Alcohol Withdrawal Induced Malignant Catatonia and Response to Bromocriptine: Case Report

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Abstract

Catatonia and malignant catatonia may result in devastating and life-threatening complications like pulmonary embolisms, pneumonia, deep venous thrombosis, rhabdomyolysis, and even death. There have been documented cases implicating alcohol withdrawal as a significant culprit in catatonia. Here, we provide a unique case report of a patient with a complicated medical course, who subsequently developed malignant catatonia secondary to severe alcohol withdrawal, and was successfully treated using both first line treatment of catatonia (lorazepam), and second-line treatment (bromocriptine). Mr. KR is a 32 year-old male with a psychiatric history significant for severe alcohol use disorder, developed fevers, rigidity and dysarthria throughout his admission despite a full negative infectious workup. He was intubated twice, he received his first doses of bromocriptine 2.5mg BID on day 29 of hospitalization. On day 30, he was extubated, and by day 31 he was afebrile, his rigidity and dysarthria had subsided, and he was able to converse coherently. Further titration of bromocriptine (up to 2.5mg every six hours on days 33-37) showed continued improvement, and the patient was eventually transferred out of the ICU. On day 37, a bromocriptine wean was initiated, which KR tolerated and showed continued

improvement with return of some baseline activities and resolution of dysarthria. This case report demonstrates the need for increased suspicion for alcohol withdrawal catatonia in patients with a complicated course of alcohol withdrawal, and illustrates a previously undocumented etiology for malignant catatonia.

Keywords
Alcohol withdrawal; catatonia; bromocriptine

1. Introduction

Catatonia is a complex neuropsychiatric disorder that was first observed and described in medical literature by Karl Ludwig Kahlbaum in his 1874 book entitled *Die Katatonie oder das Spannungsirresein*. Initially, catatonia was recognized as either an exclusive subtype of schizophrenia [1] or a form of dementia praecox [2]. However, after several different revisions, reconsiderations, and redefinitions, it is now generally regarded as its own distinct neuropsychiatric syndrome, and can be observed in psychiatric, neurologic, and/or general medical conditions. This most recent view of catatonia has not only led to a better recognition of the disease but has allowed for more effective treatments for catatonia [3]. Although its exact etiology and mechanism remains to be elucidated, it is well documented that catatonia and malignant catatonia may result in devastating and life-threatening complications like pulmonary embolisms, pneumonia, deep venous thrombosis, rhabdomyolysis, and even death [4].

There are more than 40 clinical signs and symptoms of catatonia that encompass different neuropsychiatric domains including changes in behavior, motor skills, cognition, memory, and affect. Generally, the syndrome manifests in two distinct forms: retarded-stuporous catatonia, and the less common type called excited-delirious catatonia. Multiple rating scales have been developed to 1) distinguish between the two forms and 2) assess the severity by observing and scoring several different categories such as a patient's level of excitement, immobility/stupor, mutism, staring, posturing/catalepsy, grimacing, stereotypy, mannerisms, verbigeration, rigidity, negativism, waxy flexibility, echolalia, echopraxia, and withdrawal.

Some of the more common neuropsychiatric and medical causes of catatonia include mood disorders, psychotic disorders, and medication induced. There have also been documented cases implicating alcohol withdrawal as a significant culprit in catatonia [5, 6]. More commonly, withdrawal from alcohol and benzodiazepines results in nausea, anxiety, tremors, and sweats, but can develop into alcoholic hallucinosis, delirium tremens, seizures, and in some cases death. A possible mechanism that can explain this phenomenon relates to the downregulation of GABA-A and GABA-B receptors particularly in individuals who have a history of long-term alcohol or benzodiazepine use [7, 8, 9]. In most of the cases of alcohol withdrawal catatonia, patients were successfully treated with benzodiazepines alone [5, 10-15]. Here, we provide a unique case report of a patient with a complicated medical course, who subsequently developed malignant catatonia secondary to severe alcohol withdrawal, and was successfully treated using first-line treatment of catatonia, lorazepam, and a more novel treatment, bromocriptine, given limited accessibility of ECT as a second-line treatment for malignant catatonia.

2. Case Report

Mr. KR is a 32 year-old male with a psychiatric history significant for severe alcohol use disorder and major depressive disorder. He presented to the emergency room at an outside hospital with complaints of shortness of breath and leg swelling, thought to be due to an exacerbation of the patient's congestive heart failure. On presentation, KR was tachycardic, hypoxic, hypertensive, and afebrile with a blood alcohol level of 350. The patient's last drink was documented to be about 2 hours prior to presentation.

Shortly after admission, KR decompensated with worsening tachypnea and began to exhibit severe agitation. Alcohol withdrawal protocol was initiated due to concerns of acute alcohol withdrawal, with CIWA scores ranging from 11-25. KR was treated symptomatically with lorazepam. However, despite repeated doses of lorazepam, symptoms of alcohol withdrawal persisted and a one time dose of phenobarbital was administered. KR continued to decompensate however, necessitating intubation, where he subsequently developed sinus bradycardia that progressed to asystole. Return of spontaneous circulation was achieved after approximately four minutes of cardiopulmonary resuscitation, and KR was subsequently transferred to the ICU for further management.

On day two of admission, the patient developed fevers up to a Tmax of 101.5F. KR remained febrile throughout his admission at the OSH, despite a full negative infectious workup (CT scan of the chest, abdomen and pelvis, blood cultures, sputum cultures and bronchoscopy, paracentesis and peritoneal culture, legionella antigen testing, HIV and COVID19 testing). Agitation worsened to a level requiring restraints and olanzapine administration, but without resolution of symptoms. On day 10 of hospitalization, KR had a Tmax of 103.3F. The source of fever remained unknown, and his hospital course was further complicated by the development of acute kidney injury and acute hepatic failure. Creatine kinase on day 12 was noted to be above 1,200. Transfer for liver transplant evaluation was attempted, however his medical status precluded transplant evaluation. Multiple extubation trials were attempted, without success. Ultimately the patient was transferred to our medical center on hospital day 13, for a higher level of care and hepatology evaluation.

On arrival to our medical center, KR was admitted to the ICU, intubated and sedated with a Tmax of 102.8F. Workup indicated possible aspiration pneumonia, and in the setting of continued fevers, vancomycin, aztreonam, and metronidazole were initiated for empiric coverage. Blood, urine, stool, and ascitic fluid cultures were negative. Over the course of his hospitalization, KR's kidney function improved, though liver function remained impaired. On day 17, the patient was successfully extubated.

On day 23 of hospitalization, CL psychiatry was consulted for altered mentation since extubation. Patient was noted to be confused and experiencing visual hallucinations. Initial psychiatric evaluation was significant for diaphoresis, tremulousness (more pronounced in the upper extremities), and dysarthria. The patient was able to follow commands, but the interview was severely limited due unintelligible speech secondary to dysarthria. Initial psychiatric differential remained broad, and included hepatic encephalopathy versus Wernicke's encephalopathy, neuroleptic malignant syndrome, malignant catatonia, and delirium secondary to another medical etiology. KR was started on IV thiamine 500mg TID x3 days, haloperidol 2mg

PO/IM/IV for severe agitation and to avoid benzodiazepines in the setting of possible delirium, per psychiatry recommendation.

On hospital day 24, an MRI was attempted to rule out organic neurologic causes, however the patient's tremulousness precluded the procedure. In an attempt to reduce the patient's tremulousness/agitation, haloperidol 2mg PO was given, but without success. Follow up evaluation by psychiatry revealed mild rigidity, which heightened concerns for possible catatonia. The patient was given a one time trial dose of lorazepam 2mg IV with minimal response. A rapid response was called later that day for tachycardia and tachypnea; KR subsequently required re-intubation and transfer back to the ICU for escalation of care. A trial of cyproheptadine was initiated, due to concerns for serotonin syndrome given rigidity and hyperreflexia with associated fevers. Several days of treatment with cyproheptadine did not result in improvement of symptoms and the patient remained intubated and febrile. Given the lack of improvement, the patient's significant alcohol history, evidence of severe alcohol withdrawal prior to transfer to our medical center, and possible worsening of symptoms after receiving haloperidol, psychiatry suspected that the patient's persistent symptoms may be due to malignant catatonia secondary to alcohol withdrawal. Lorazepam was reconsidered, however given the patient's deterioration status post lorazepam administration, the recommendation to begin bromocriptine and pursue transfer for ECT treatment was made given the concern for malignant catatonia.

KR received his first doses of bromocriptine 2.5mg BID on day 29 of hospitalization. On day 30, he was extubated, and by day 31 he was afebrile, his rigidity and dysarthria had subsided, and he was able to converse coherently. Further titration of bromocriptine (up to 2.5mg every six hours on days 33-37) showed continued improvement, and the patient was eventually transferred out of the ICU. On day 37, a bromocriptine wean was initiated, which KR tolerated and showed continued improvement with return of some baseline activities and resolution of dysarthria.

ECT transfer proved exceedingly difficult secondary to the patient's complicated medical status. Dosing and frequency of bromocriptine was adjusted based on symptomology and monitoring of vital signs while awaiting for transfer. On hospital day 41, the patient was restarted on lorazepam for further coverage of catatonia. Bromocriptine weaning was attempted, however it resulted in re-emergence of fevers; ultimately, KR was placed on a regimen of bromocriptine 10mg every six hours, and lorazepam 1mg every six hours. Ultimately, KR was transferred to a medical-psychiatric unit with ECT capabilities on day 53.

3. Discussion

This case report illustrates a severe case of alcohol withdrawal malignant catatonia resulting in acute multiorgan dysfunction, intubation and prolonged hospitalization. The complicated presentation and difficulty in diagnosis in this patient illustrates the often overlooked nature of this condition, especially in the setting of alcohol withdrawal, as well as the number of diagnoses that may mimic malignant catatonia and can contribute to misdiagnosis and ineffective treatment.

Few reports of alcohol withdrawal catatonia exist in the present literature, as it is a notably uncommon cause of catatonia. It is marked by the typical signs of catatonia, but often only after a prolonged course of alcohol use [6]. Previous studies suggest that the structure of a brain under chronic alcohol consumption shows striking similarities to that of a catatonic brain: both show

marked abnormalities in GABA-nergic signaling in the cortical regions of the brain [6]. A possible mechanism that has been proposed by Lander *et. al* [8] and Carrol [7] relates to the downregulation of GABA-nergic pathways, in particular with the GABA-A receptor. Given its action on GABA-nergic pathways, it is possible that alcohol withdrawal could sensitize the brain to benzodiazepine withdrawal catatonia, especially as benzodiazepines are tapered as alcohol withdrawal resolves [5]. Several studies have shown how alterations in GABA-nergic pathways, specifically along the parietal cortex, orbitofrontal cortex, ventromedial prefrontal cortex, and the dorsolateral prefrontal cortex can produce symptoms of catatonia [16-18]. In a case report of catatonia attributed to withdrawal from benzodiazepines by Carroll [7], it is suggested that baclofen cessation may have been a contributing factor. This case report further hypothesizes a role for GABA-A and GABA-B activity in catatonia, as benzodiazepine withdrawal may result in a decrease in GABA-A agonist activity, which was then worsened due to decline in GABA-B activity from baclofen withdrawal. This further supports that an imbalance of GABA receptors may result in catatonia. In addition to its actions on GABA-nergic pathways, alcohol also induces its effects on NMDA receptors and dopamine receptors, both of which have been implicated in the development of catatonia [19, 20]. The roles of these receptors in catatonia have been shown in studies involving the successful treatment of catatonic patients with amantadine (an NMDA-receptor antagonist), and the propensity of patients with anti-NMDA encephalitis to develop catatonia [21-23].

Malignant catatonia is defined as catatonia with hyperthermia and autonomic instability [24]. To our knowledge, no explicit episodes of malignant catatonia related to alcohol withdrawal have been reported in the literature. Our patient KR met multiple criterias for malignant catatonia including autonomic instability (fevers, tachycardia), movement abnormalities, and cognitive changes. However, the exact etiology of the malignant features in patient KR remained unknown, but was likely multifactorial given the complexity of his case.

Patient KR had received one dose of olanzapine early in his hospital course for agitation suspected to be secondary to alcohol withdrawal. Prior to the administration of Olanzapine, KR had already displayed signs and symptoms of catatonia, and the introduction of a dopamine antagonist could have precipitated the transformation of catatonia into malignant catatonia. On the other hand, given the persistent fevers prior to Olanzapine administration, one can conclude that KR was already in a state of malignant catatonia, and the addition of an antipsychotic only served to exacerbate his condition. KR additionally received one dose of haloperidol later in his hospital course, also for agitation - this resulted in symptoms of mild rigidity developing. This in combination with persistent fevers provides further evidence that KR was likely experiencing underlying malignant catatonia throughout his hospital course, beginning on day two of admission with the initial onset of fevers.

In previously reported cases of non-malignant alcohol withdrawal catatonia, patients had an excellent response to benzodiazepines, which is the first line treatment in non-malignant, non-alcohol withdrawal catatonia [6]. KR however, did not respond to benzodiazepines upon admission and presentation of his symptoms. The gold standard therapy for malignant catatonia is electroconvulsive therapy (ECT) [25], which is thought to increase the GABA-nergic activity in the brain, and is reported to be 80-100% effective in reversing symptoms [26]. Though ECT is considered first line treatment for malignant catatonia, it is not universally available, and poses a potential challenge for access to treatment, which is demonstrated by our case.

There remains little definitive information other than case reports on alternative treatments for malignant catatonia or alcohol induced catatonia. A case report from Mahmood in 1991 describes a detailed case of a catatonic patient who was successfully treated with bromocriptine, though most other reports of its use are anecdotal, and none were used in the setting of alcohol withdrawal [27]. Bromocriptine falls under the dopamine receptor agonist class of drugs, and acts as a selective D2 receptor agonist and partial D1 receptor antagonist in the brain [28]. Though the pathophysiology of catatonia remains unknown, one of multiple theories proposed is a striatal D2 receptor blockade, which could explain bromocriptine's possible effectiveness in the treatment of catatonia [28]. It has been well documented that D2 antagonists have induced catatonia or worsened symptoms of existing catatonia, which supports a role of dopamine dysfunction in the illness [24].

Diagnosis of alcohol withdrawal catatonia in patients already receiving treatment for alcohol withdrawal can be especially difficult, as proven in our case, as conditions such as hepatic encephalopathy and Wernicke/Korsakoff syndrome also have to be ruled out. Malignant catatonia outside of the alcohol withdrawal spectrum is often diagnosed late in its course due to its similar presentation to a number of different conditions, as earlier described. As no distinct biomarkers presently exist for malignant catatonia, it is often a diagnosis of exclusion, after exhausting other medical diagnoses. It has been proposed that the high mortality in malignant catatonia is related to delay in recognition and treatment. Complications secondary to malignant catatonia also delay prompt diagnosis, as high fevers and cardiopulmonary demise can steer clinicians towards an infectious or autoimmune etiology. These difficulties in diagnosis and medical complexity of malignant catatonia are certainly represented in our case report, as evidenced above.

This case report demonstrates the need for increased suspicion for alcohol withdrawal catatonia in patients with a complicated course of alcohol withdrawal, and illustrates a previously undocumented etiology for malignant catatonia. Additionally, this case highlights the need for definitive alternative management of malignant catatonia as not all hospitals have ECT capabilities, and those patients who may not be candidates for ECT face life-threatening challenges.

Author Contributions

Schumaker A, Klauber R, Aasen M, Padua M, Meresh E drafted the manuscript, contributed in manuscript writing, reviewed literature, provided feedback, revised and edited the manuscript.

Competing Interests

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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