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Case Report

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A Case of Myotonia Congenita and Schizophrenia: Difficulties in Treatment with Antipsychotics due to Hypersensitivity to Extrapyramidal Symptoms

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Abstract

Myotonia congenita is a rare non-dystrophic skeletal muscle disease characterized by an inability to relax skeletal muscles after abrupt voluntary movements. Patients with this condition have stiff muscles and difficulty with mobility, especially when initiating movement after periods of rest. It is well known that movement disorders are a common side effect of antipsychotics due to their ability to antagonize dopamine 2 receptors in the extrapyramidal part of the basal ganglia. The purpose of this case is to describe the effects antipsychotics had on a 59-year-old Caucasian male with comorbid myotonia congenita and schizophrenia in an inpatient psychiatric hospital setting. Medication trials of ziprasidone, haloperidol and clozapine exacerbated his myotonic symptoms leading to falls and complaints of severe muscle stiffness, which were relieved upon discontinuation of all antipsychotic medications. This suggests that patients with myotonia congenita may have an increased sensitivity to the extrapyramidal side effect profile of antipsychotics. Treatment options for this patient case are discussed with an emphasis on lamotrigine.

Keywords: Myotonia congenita; Schizophrenia; Myopathy; Antipsychotics; Extrapyramidal symptoms

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Introduction

Myotonia congenita (MC) is a non-dystrophic myopathy in which there is impaired relaxation of striated muscle groups after voluntary contraction [1]. The main, and most widely studied, contributing mutation to this muscle

disorder is that of the CLC-1 gene [2]. This mutation results in irregular slow-gated Cl⁻ channels; a channel widely responsible for reducing membrane excitability in muscle cells and stabilizing the resting membrane potential. Altered chloride channels predispose muscle tissue to spontaneous action potentials, also called myotonic “runs”, leading to

impaired muscle relaxation and therefore prolonged muscle contraction [2]. Any skeletal muscle can be affected, although it occurs most often in the legs [1]. These patients typically present with muscle hypertrophy [1]. Patients with myotonia congenita report that muscle stiffness tends to improve after repeated muscle movements, oftentimes referred to as the warm-up effect [1]. Julius Thomsen, the scientist who first distinguished Thomsen's disease from Becker's disease (the two types of myotonia congenita) in 1876, had believed there may be a possible association between myotonia congenita and psychosis as both conditions were present in his family. Results from a literature search conducted via PubMed did not validate this belief, however multiple cases of comorbid myotonia congenita and psychiatric disorders have been published [3-5].

Antipsychotics are first line treatment for schizophrenia. All antipsychotics, with the exception of clozapine, often reserved for treatment-resistant schizophrenia, show similar efficacy in reducing psychotic symptoms, however they all differ in terms of their side effect profile [6]. Extrapyramidal symptoms (EPS) are a well-known side effect of antipsychotics due to their substantial dopamine 2 (D2) receptor blockade in the nigrostriatal dopamine (DA) pathway. Drug toxicity, and therefore EPS, begins to occur when approximately 80% of D2 receptors in the nigrostriatal pathway are blocked, whereas therapeutic efficacy is achieved when approximately 60% of D2 receptors are occupied [7]. First generation antipsychotics cause more extrapyramidal side effects than the second generation (also referred to as atypical) antipsychotics due to their relatively higher affinity for D2 receptors compared to serotonin receptors. Atypical antipsychotics have a higher affinity for serotonin receptors which somewhat mediates dopamine blocking ability in this pathway [8]. Although second generation antipsychotics generally have a lower incidence of EPS, aripiprazole,

quetiapine, and clozapine specifically have the lowest incidence within this drug class [9]. The four types of EPS include dystonia, akathisia, pseudoparkinsonism, and tardive dyskinesia.

A 59-year-old Caucasian male presented to an inpatient psychiatric hospital with both uncontrolled schizophrenia and myotonia congenita, as well as a possible seizure disorder. We observed that controlling his psychiatric symptoms was difficult due to his heightened sensitivity to EPS. Here we will present and discuss his psychiatric pharmacologic history with an emphasis on the difficulties that a comorbid myotonia presents, as well as offer an approach to managing both conditions effectively.

Methods

All pertinent medical data on M.N. was retrieved from the hospital's electronic medical record system, TIER, from the time the patient was admitted in February, 2019 through the end of August, 2019. The patient's progress and his response to medication therapy was reviewed with the unit's psychiatrist and medical team during weekly treatment team meetings. Additionally, data regarding the patient's family history and past medical history was obtained in two separate in-person interviews. The four researchers took approximately 3.5 months to collect all available data, which was then thoroughly analyzed in order to compile this case study.

Furthermore, a literature search was conducted in PubMed, Medline, and Embase databases, and included MeSH terms such as "myotonia congenita", "Thomsen's disease", "Becker's disease", "psychosis", "schizophrenia", and "extrapyramidal symptoms". Six studies were identified, of which three met criteria and were subsequently analyzed to provide background information. The search was limited to human cases of which articles were accessible and were either published in English or had

available English abstracts. Publication year was not a limiting factor in this search. The purpose of the literature search was to assess whether there was a true correlation between myotonia congenita, psychosis, and treatment with antipsychotics.

Case Presentation

A 59-year-old Caucasian male, M.N., presented to a long-term inpatient psychiatric hospital as incompetent to proceed with charges he had faced which were rooted in fixed delusional ideas due to uncontrolled schizophrenia. The patient had a known history of myotonia congenita since childhood, and displayed hallmark signs of the disease during his initial comprehensive psychiatric and medical history evaluation. For example, M.N. required staff to assist him back to a standing position at the end of this interview. The patient had been evaluated by both the psychiatrist and internist physician to confirm these diagnoses. Additionally, one seizure was reported in his medical history, prompting a diagnosis of unspecified epilepsy without status epilepticus. The patient has no other comorbid diagnoses and no known drug allergies. He has had two previous psychiatric hospitalizations, each four years apart, and one non-psychiatric-related hospital admission to treat a brain hemorrhage due to a fall. The patient denied any alcohol or substance abuse, and expressed fixed delusions that he is a member of the FBI. He has a family history positive for mental illness as his mother committed suicide when M.N. was a child. Further information about his family is difficult to confirm, as the patient's condition makes him a poor historian.

Upon admission, the patient was prescribed ziprasidone 100mg daily to control his psychosis, and levetiracetam 500mg twice daily for seizure prophylaxis. There was no significant improvement in his psychiatric status, as evidenced by his Brief Psychiatric Rating Score (BPRS) taken during monthly

psychiatric evaluations with the psychiatrist. Therefore, haloperidol 5mg twice daily was initiated one month later to augment the antipsychotic action of ziprasidone. Less than another month later the patient was started on diphenhydramine 25mg twice daily in an attempt to alleviate major stiffness in his legs; a side effect from the antipsychotics thought to be further exacerbated by the underlying myotonia congenita. Complaints of stiffness and gait abnormalities persisted, so diphenhydramine was discontinued and substituted for benztropine 2mg twice daily. Within a week after the switch to benztropine, the patient suffered his second fall while being at the hospital; the psychiatrist noted that the EPS seemed to be worsening his pre-existing myotonia. As a result, ziprasidone, haloperidol, and benztropine were all discontinued approximately 3 months after admission. At this point in time the patient was on levetiracetam 500mg twice daily, diphenhydramine 25mg twice daily, and acetaminophen 325mg as needed for back pain possibly due to his MC. The patient's psychiatric status declined, as evidenced by a worsening in the BPRS score from a 31 to a 38. On the other hand, in an interview M.N. expressed improvement in muscle rigidity following the discontinuation of all antipsychotics. Notably, he was able to stand up and open his fists comfortably during this interview which he was unable to do while on the antipsychotics. During the interview, M.N. additionally stated that past attempts to treat his myotonia included trials of both mexiletine and tocainide. He expressed that mexiletine was ineffective in controlling his muscle stiffness, however tocainide was effective but he had to stop using it because it was "killing people". Interestingly, the patient stated that he feels his MC has improved since beginning levetiracetam for seizure control.

Two months after discontinuing ziprasidone and haloperidol (M.N. was without any antipsychotic medication for two months), the

antipsychotic clozapine was initiated. This medication was selected due to its low association with EPS; a favorable side effect profile specifically for this patient. All pertinent labs were within normal limits in order to safely initiate clozapine. Approximately three weeks after initiating clozapine, the patient's mental status had improved with a new BPRS score of 34 in addition to a patient statement saying he had "resigned" from the FBI. However, the patient had become noticeably weaker and unsteady since beginning clozapine. He had great trouble walking and rising from a seated position. He then suffered a third fall while getting out of bed and was sent to the emergency department for a contusion on his forehead; CT scan was unremarkable. Despite an improvement in psychiatric status, clozapine was discontinued approximately three weeks after initiation due to his deteriorating physical state. Approximately two weeks after clozapine was discontinued, M.N.'s motor function had significantly improved once again. However, he also expressed a renewed belief that he was in the FBI, indicative of uncontrolled schizophrenia.

Conclusion

Clinical assessments from various healthcare professionals within the inpatient psychiatric hospital suggest that treating M.N.'s schizophrenia is further complicated by his comorbid myotonia congenita, which may be related to his heightened sensitivity to extrapyramidal side effects of antipsychotic medications. Even clozapine, which has some of the lowest incidences of EPS within the second generation antipsychotic class, caused severe muscular side effects in this patient. It was clear that the patient's myotonia had worsened significantly from clozapine, however it is unclear whether the fall, specifically, was due to myotonia or orthostatic hypotension, which is one of the five boxed warnings of clozapine. This treatment failure is important to keep in mind since it would be

expected that clozapine, quetiapine and aripiprazole would all be safer treatment options for this unique patient type. Quetiapine and aripiprazole have not yet been trialed in this patient. Close monitoring for falls is crucial if M.N.'s healthcare team does decide to initiate these in the future.

Discussion

Myotonia congenita is a rare disorder with a worldwide prevalence of 1:100,000, and as such, there is limited research on treatment options for this disorder [1]. Currently, there are no FDA-approved treatments for myotonia congenita and current treatment options depend on the severity of symptoms. For mild cases, lifestyle changes may be sufficient [3]. Pharmacologically, sodium channel blockers comprise some of the more commonly used drugs to treat MC [1]. Mexiletine, lamotrigine, ranolazine, procainamide, tocainide, and phenytoin are some treatment choices that have been used off-label to control MC [10]. Notably, tocainide was taken off the US market in 2003 due to serious and potentially fatal hematological adverse effects [11].

Mexiletine and lamotrigine, some of the more widely studied treatment options for MC, both block sodium channels to prevent an influx of sodium ions, and therefore decrease the rate of rise, and amplitude, of action potentials, allowing muscle cells to more easily regain resting membrane potential [12,13]. With less action potentials, the affected muscles are less prone to myotonic runs and prolonged contractions. Decreasing action potentials by any means has shown to be an important mechanism in the ability of myocytes to relax after a voluntary contraction in the case of myotonia congenita. Levetiracetam, the drug M.N. believes has improved his myotonic symptoms, is not typically studied in the context of MC. Levetiracetam's mechanism of action is to bind to synaptic vesicle protein SV2A in the brain which reduces the rate of

synaptic neurotransmitter release and ultimately results in less action potentials [14]. However, it is vital to note that behavioral problems such as anger, emotional lability, neurosis, aggression and psychosis, are well known side effects of levetiracetam with an occurrence of approximately 10.1% in adults [15]. This side effect profile may be unfavorable for psychiatrically unstable patients; nonetheless, benefit versus risk must always be assessed on an individual basis.

Lamotrigine, another agent studied for its positive effects in patients with MC, is FDA-approved for focal and generalized seizures, and bipolar disorder. Andersen, Hedermann, and Witting et al., conducted a phase II randomized, double-blind, placebo-controlled, two-period crossover study in which lamotrigine was the intervention for 26 patients with non-dystrophic myotonias [13]. Lamotrigine 25mg daily, 50mg daily, 150mg daily, then 300mg daily were each given for two weeks successively, with a one-week washout period directly followed by 8 weeks of placebo. Titration was necessary due to lamotrigine's boxed warning for serious skin rashes. The study's primary outcome of reduction in severity scores via the Myotonic Behavior Scale were significant [13]. Secondary outcomes in reducing physical timed tests regarding motions of the eye, hand and legs were also significant [13]. The most common side effect experienced was headache [13].

Given lamotrigine's perceived efficacy in MC, in addition to controlling mood and seizures, we inquire whether this medication would have additional positive effects on his epileptic and psychiatric status while improving the patient's MC. The initiation of lamotrigine before attempting additional trials of alternative antipsychotics may be an appropriate approach to addressing M.N.'s myotonia congenita. It may also have possible positive effects on mood disorder components featured in

schizophrenia. He is currently responding well to levetiracetam and has not suffered a seizure since its initiation. Therefore, the choice of whether to add lamotrigine to his regimen (risk of additive central nervous system effects), or to cross-taper from levetiracetam to lamotrigine would be up to his treatment team.

An important limitation to this case is that the patient's medical record is likely not all inclusive of his complete medical history, especially dating back to childhood. Additionally, M.N. is not a fully reliable historian due to his mental illness. Another limitation is that his case was evaluated for a relatively short period of 3.5 months.

Further research needs to be done in the area of myotonia congenita, especially with regards to its response to medications that cause EPS and the possibility of worsening the condition. It is suitable to suggest a safety and efficacy clinical trial with lamotrigine as the intervention of choice for subjects with comorbid schizophrenia and myotonia congenita. As these two comorbidities are rare, a special emphasis should be placed on reporting case studies of this patient population. Healthcare professionals caring for patients with MC taking antipsychotics are encouraged to share their findings so that we can move toward a more conclusive statement on whether MC heightens sensitivity to extrapyramidal symptoms and how to better manage these issues.

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