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Review

Catatonia Following Cessation of Topiramate in a Patient with Prader-Willi Syndrome: Case Report and Review of Literature

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Abstract

Case studies have associated catatonia with withdrawal from benzodiazepines and clozapine, both of which have been shown to increase GABA activity. Long-term use of GABAergic medications could result in GABAA downregulation and sudden discontinuation of the GABAergic drug could lead to a GABA hypoactive state which could predispose the patient to catatonia. The anticonvulsant topiramate, is known to increase brain GABA activity. Prader-Willi syndrome (PWS) is a genetic imprinting disorder characterized by lack of expression of genes in the paternal chromosome 15q11-q13, resulting in neonatal hypotonia, small hands and feet, almond-shaped eyes, hypogonadism, short stature, excessive hunger, obesity, diabetes, and sometimes behavioral phenotypes, including catatonic symptoms, stereotypies,

compulsive self-injury, excessive sleepiness or unresponsiveness, and psychosis. Prader-Willi syndrome (PWS) is associated with catatonia and is linked to GABA system abnormalities. A reduction in GABA transmission could be responsible for the neuropsychiatric complication like catatonia. We report a case of PWS who developed catatonia after cessation of Topiramate.

Keywords
Prader-Willi syndrome; topiramate; catatonia; GABA; lorazepam; bromocriptine

1. Introduction

The literature reveals an association between withdrawal from benzodiazepines and clozapine with catatonia as both withdrawals lead to increased GABA activity in the CNS [1-4]. Long-term use of GABAergic medications results in $GABA_A$ downregulation, thus a sudden discontinuation of a pro-GABAergic medication may lead to a GABA hypoactive state which could predispose a person to develop catatonia [5]. The anticonvulsant topiramate, is also known to increase brain GABA activity [6]. Prader-Willi syndrome (PWS) is a genetic imprinting disorder characterized by lack of expression of genes in the paternal chromosome 15q11-q13, resulting in neonatal hypotonia, small hands and feet, almond-shaped eyes, hypogonadism, short stature, excessive hunger, obesity, diabetes, and at times behavioral phenotypes manifesting as catatonic symptoms, stereotypies, compulsive self-injury, excessive sleepiness or unresponsiveness, and psychosis [7, 8]. Prader-Willi syndrome (PWS) is associated with catatonia and is linked to GABA system abnormalities [9-11]. Thus, a reduction in GABA activity due to the cessation of a pro-GABA agent could be responsible for the development of a neuropsychiatric disorder such as catatonia [12]. Here we report a case of a patient suffering from PWS who developed catatonia after cessation of topiramate.

2. Case Presentation

Mr. H a 24 year old Asian American man was admitted to the internal medicine service of our institution for hyperglycemia and altered mentation after being sent from an outside psychiatric hospital to our emergency department for acute medical evaluation of unresponsiveness with a reported blood glucose of over 400 mg/dL (22.2 mmol/L). Mr. H was receiving psychiatric care at the outside psychiatric hospital for worsening agitation that surpassed the capabilities of his group home. Medical history was significant for type I Diabetes Mellitus on insulin therapy since early childhood, bipolar disorder, and Prader-Willi syndrome. Initial physical examination was unremarkable apart from multiple yellow ecchymosis (skin discoloration from bleeding) on Mr. H's mid-sternum and upper and lower extremities along with hypotension, tachycardia, and an intermittently obtunded mental status with minimal verbal responses every few hours. Of note, he told nursing that the outside psychiatric hospital had "overdosed" him with medications to make him sleepy. Initial laboratory findings revealed elevation in lactate (3.2 MM/L), glucosuria (3+), and small ketonuria for which fluids and broad spectrum antibiotics were given until further work-up was negative for diabetic ketoacidosis, a hyperosmolar hyperglycemic state, thyroid dysfunction, renal-hepatic dysfunction, blood cell indices abnormalities, metabolic derangements, urino-

pulmonary infections, cerebro-vascular accidents, illicit substance intoxication, alcohol intoxication, bacteremia, and fungemia.

Medication reconciliation revealed Mr. H was receiving the following prior to presentation to our institution: fluoxetine 20 mg by mouth every morning, clonidine 0.2 mg by mouth three times a day, clonazepam 1 mg by mouth twice a day, quetiapine 100 mg by mouth in the morning and afternoon and 400 mg by mouth at bedtime, topiramate 100 mg by mouth twice a day, insulin aspart sliding scale, metformin 1000 mg by mouth twice a day, linagliptin 5 mg by mouth every morning, and simvastatin 20 mg by mouth at bedtime. It was noted that the medical service in the outside psychiatric hospital was attempting to transition Mr. H from insulin therapy to combination metformin and linagliptin before presentation. On admission to our institution Mr. H was continued on quetiapine 100 mg by mouth in the morning and afternoon and 400 mg by mouth at bedtime, fluoxetine 20 mg by mouth every morning, topiramate 100 mg by mouth twice a day, and started on glargine 8 units every morning along with lispro 2 units three time a day with meals and additional sliding scale lispro three times a day with meals (2 units if pre-meal glucose 180-210 mg/dL (10.1-12.0 mmol/L), 3 units if pre-meal glucose 211-260 mg/dL (12.1-14.4 mmol/L), 5 units if pre-meal glucose 261-310 mg/dL (14.5-17.1 mmol/L), 7 units if pre-meal glucose 311-360 mg/dL (17.2-20 mmol/L), and 9 units if pre-meal glucose is greater than 360 mg/dL (20.0 mmol/L).

A rapid response team was called early during his admission for unresponsiveness while on the general medical floor resulting in transfer to the ICU with subsequent normal arterial blood gas and no clinical response to naloxone. Neurology was consulted in the ICU to rule out seizure activity due to identification of horizontal nystagmus and pupillary oscillation for which lorazepam 2 mg IV was given twice without any clinical change. Physical examination revealed an unresponsive state with intact corneal reflex, intact pharyngeal reflex, and symmetric/normoactive reflexes. A stroke code was called resulting in patient intubation for airway protection with the use of propofol for sedation. Blood glucose at the time of stroke code was 363mg/dL (20.14 mmol/L). Fluoxetine, quetiapine, and topiramate were withdrawn at that time. Work up only revealed slight hyperammonemia (72 ug/dl), hyperprolactinemia (31 ng/ml), continued glucosuria and ketonuria, with normalization of ammonia within 24 hours. CT head without contrast, CT head and neck angiography with and without contrast and CT head perfusion with and without contrast were all negative for acute findings. Twenty Four hour video EEG revealed delta and beta wave activity while the patient was sedated and a posterior dominant rhythm once sedation was weaned, though activating maneuvers were not completed. Given negative EEG findings for epileptiform activity, patient was transitioned from propofol to dexmedetomidine.

Consultation-Liaison Psychiatry (CL) was then consulted at the recommendation of neurology to rule out catatonia. After extubation (and discontinuation of all sedation), Mr. H demonstrated mutism, was nonresponsive to verbal and painful stimuli, rigid on flexion and extension of upper and lower extremities and was observed posturing his upper extremities in an odd fashion. Psychiatrists more routinely make use of the Bush-Francis Catatonia Rating Scale for the diagnosis and management of catatonia, though this scale was not utilized in our patient. The Glasgow Coma Scale (GCS) [13] is a lifesaving tool used by our colleagues in the general hospital when assessing for coma, especially in the ICU setting. Patient initially presented with verbal (confusion) and eye (opens eyes in response to voice) deficits on his GCS (Table 1) which correlate with mild deficits of immobility/stupor, mutism, staring, and withdrawal in the Bush-Francis Catatonia Rating Scale [14]. By day 4, when his first RRT was called, he had a sudden drop in GCS to 3 which would correlate

with severe deficits of immobility/stupor, mutism, staring, and withdrawal in the Bush-Francis Catatonia Rating Scale, denoting the development of severe catatonia.

Table 1 Progression of Glasgow Coma Scale scores during hospitalization.

GCS (comments)	Day 1	Day 3	Day 4	Day 5-8	Day 8-24
Presentation to ED	E3M6V4: GCS 13				
All day		E4M6V5: GCS 15			
At 0800			E4M6V5: GCS 15		
RRT #1 for unresponsiveness at 1615			E1M1V1: GCS 3		
At 1800 after lorazepam 2 mg IVx2 at 1621 and 1629 for "seizure" activity			E3M6V1: GCS 10		
All days				GCS ≤ 11	
All days					GCS ≥ 14

** GCS was not documented during RRT#2 on Day 12.

** Clonidine and clonazepam were never started at our institution (discontinued on presentation to our ED).

** Last doses for quetiapine and fluoxetine were on Day 4.

** Last dose for topiramate was on Day 5.

Mr. H received 2 mg IV lorazepam with noted improvement in posturing and rigidity, thus lorazepam 1 mg IV every 6 hours was initiated. However, significant agitation resulted in near removal of IV access thus necessitating initiation of valproic acid with up-titration to 500 mg IV twice daily. C/L Psychiatry then recommended MRI brain with and without contrast to rule out other structural causes of catatonia which revealed increased T2/Flair in the white matter posterior to the atria of the bilateral lateral ventricles as well as scattered punctate T2/Flair hyperintensities within the posterior left frontal lobe white matter. Our inpatient neurology colleagues noted that these white matter changes appeared chronic in nature, thus further work-up of these changes was deferred to their outpatient clinic. However, there are imaging studies looking at cortical and white matter changes in patients afflicted with PWS that show cortical changes in the medial prefrontal cortex and dorsolateral prefrontal cortex (which are postulated to be associated with the disinhibition and hunger found in PWS patients that leads to obesity), and cortical changes around the anterior cingulate cortex (which are posited to be associated with executive control of behaviors to stimuli begetting a mismatch in cognitive and emotional processing resulting in the overeating seen frequently in PWS) [15]. Thus, the white matter/cortical changes seen in our patient were more readily attributed to structural changes seen in patients afflicted with PWS and did not readily explain his catatonic presentation.

The primary service then changed IV lorazepam to IV diazepam after 4 days of lorazepam treatment after which creatinine kinase became elevated. C/L Psychiatry then re-started lorazepam

and repeat, higher ammonia levels resulted in discontinuation of valproic acid (after 5 days of receiving this valproic acid).

Slow improvement in catatonia allowed for switch to oral lorazepam, however, a second rapid response team was called for unresponsiveness after patient missed 3 of his last 4 scheduled oral lorazepam doses after which IV lorazepam was re-initiated though catatonia did not respond at that time. Bromocriptine was thus initiated in addition to lorazepam for treatment of catatonia. Topiramate was also re-initiated by the C/L Psychiatry service, though home clonidine, clonazepam, fluoxetine, and quetiapine were not restarted.

The patient was eventually discharged after 24 days in our institution back to the outside psychiatric hospital on a 6 month oral lorazepam taper, 2 week bromocriptine taper, and topiramate up-titration. Of note, electroconvulsive therapy (ECT), an effective treatment for catatonia [16, 17] was unable to be utilized in this case due to institutional unavailability and the patient was unable to be transferred to an outside institution with ECT capabilities during his hospitalization.

3. Discussion

O'Regan and colleagues have published a case report of a patient afflicted with catatonia whom initially presented with a GCS drop from "15 to 6 (E1M4V1)" which led to intubation and extensive work up for coma; much like the presentation of our patient [18]. Ajmal also describes a case series of two patients whom similarly presented with a sudden drop in GCS to 3 and 5, respectively, were intubated, and had subsequent extensive work up revealing dissociative states [19]. Thus, catatonia (and similarly presenting but clinically unrelated dissociative states) should remain in the differential diagnosis when assessing for coma after identification of a low GCS [20].

Catatonia is a neuropsychiatric condition characterized by the inability to perform normal movements in the context of underlying psychiatric, medical, neurologic, and drug-induced problems. Catatonia can present with hypoactive or hyperactive subtypes, as well as the severe and potentially fatal subtype known as malignant catatonia. While the full pathogenesis remains unclear, it is thought that GABA hypoactivity plays a role, given the therapeutic efficacy of benzodiazepines [5]. Moreover, some case studies have associated catatonia with withdrawal from benzodiazepines and clozapine, both of which have been shown to increase GABA activity [1-4]. In this model, long-term use of GABAergic medications could result in $GABA_A$ downregulation. Subsequently, upon sudden discontinuation of the GABAergic drug, an individual lapses into a GABA hypoactive state which could predispose the patient to catatonia [5]. The efficacy of ECT as an effective treatment of catatonia also supports that GABA hypoactivity model, since ECT increases serum GABA levels and $GABA_B$ activity [21, 22].

Interestingly, Prader-Willi syndrome (PWS) is associated with catatonia and is linked to GABA system abnormalities [9-11]. A cluster of $GABA_A$ receptor subunit genes exists within the 15q11-q13 hypermethylated region, potentially predisposing PWS patients to GABA hyposensitivity and consequently increasing their risk for catatonia [23]. 15q11-q13 genes have also been associated with catatonic schizophrenia and autism, suggesting a potential genetic link between catatonia, autism, and PWS [24, 25]. A reduction in GABA transmission could therefore be responsible for the neuropsychiatric complications seen in PWS [12].

The anticonvulsants topiramate, carbamazepine, and valproic acid are known to increase brain

GABA activity and have been posited to reverse catatonia in multiple case reports [6, 26, 27]. Moreover, a case report has documented catatonia following abrupt cessation of oxcarbazepine in a patient with PWS [28]. Catatonia from topiramate withdrawal is not so certain in this case. Topiramate, fluoxetine, quetiapine were withdrawn shortly after the admission, and there could be additional causes for catatonia. Fluoxetine withdrawal typically leads to serotonin discontinuation syndrome and not catatonia. Risk of serotonin discontinuation syndrome is lowest for fluoxetine as it's metabolite norfluoxetine's half life is more than 2 weeks [29]. In their review of withdrawal catatonia, benzodiazepine withdrawal was the most associated [30]. Among the anti-psychotics, clozapine was the most associated [30]. As per Lander et al, other anti-psychotics are not known to cause withdrawal catatonia.

Abrupt discontinuation of Quetiapine is associated in a few case reports with nausea, vomiting, dizziness, similar to discontinuation of SSRIs. The case reports hypothesis that the D2, 5HT-1a and H1 receptors are part of the milieu that creates the withdrawal effect. One case report [31] showed discontinuation from 100 mg of Quetiapine that was not responsive to ondansetron. Finally the patient was given Compazine during a slow taper. This lead to their hypothesis that D2 and H1 were involved in the discontinuation syndrome observed. Another case report [32] reported a similar case and came to similar conclusions regarding the receptor profile that is driving the discontinuation syndrome. There were no studies found where discontinuation of quetiapine induced a catatonic like syndrome.

Therefore, we hypothesize that the abrupt cessation of topiramate in our patient with PWS (whom is already susceptible to GABA system dysregulation) most likely led to the development of catatonia.

To our knowledge, this is the first case report documenting a prolonged course of catatonia following abrupt cessation of topiramate. In our patient, after the initial stroke code was called during his admission for hyperglycemia (hospital admission day 4), topiramate was withdrawn**.** On hospital admission day 6, psychiatry was consulted for catatonia. We thus theorize that topiramate's GABA stimulation acted as a protective factor against the development of a prolonged course of catatonia in our patient, which was only worsened by the successive switches from IV to oral lorazepam and from lorazepam to diazepam. Drug history of patient is included as a graphic abstract [33] (Figure 1).

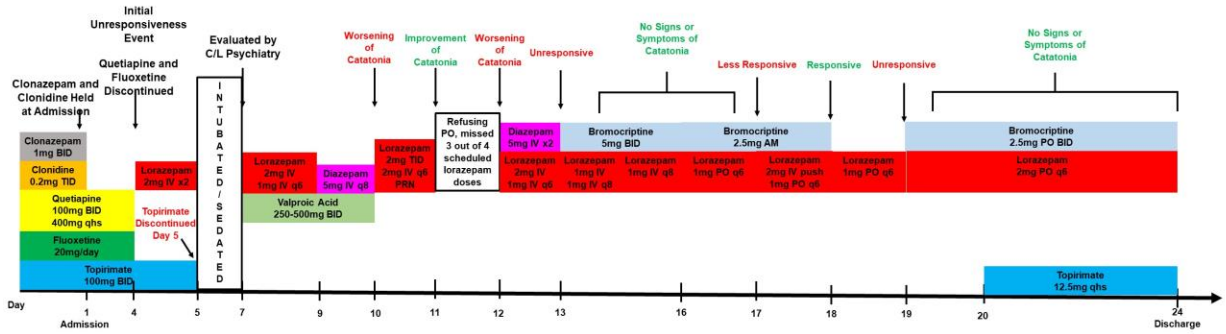

Figure 1 Drug history.

Though, we must also consider the cessation of valproic acid also theoretically resulting in a further decrease in protective GABA activity. Our patient ultimately improved with lorazepam and bromocriptine as topiramate was re-started towards the end of our patient's hospitalization on our

general hospital floor.

Precipitating prolonged catatonia in high risk and vulnerable patients with underlying states predisposed to GABA dysfunction must be taken into consideration when medications such as topiramate, oxcarbazepine, benzodiazepines, and valproic acid are abruptly discontinued. Additional studies are needed to further elucidate the role GABA modulating or inhibiting medications play in the precipitation and treatment of catatonia outside of benzodiazepine class medications such as lorazepam.

Author Contributions

All authors equally contributed to the preparation of manuscript, literature review and edition.

Competing Interests

The authors have declared that no competing interests exist.

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