A Complex Presentation of Pediatric Neuroleptic Malignant Syndrome Related to Polypharmacy in a 12-Year-Old Male

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To The Editor:

NEUROLEPTIC MALIGNANT SYNDROME (NMS) IS A RARE, life-threatening side effect of medications impacting dopamine. In 1960, Delay and colleagues first documented symptoms of severe muscle rigidity and hyperthermia related to the use of haloperidol (Delay et al. 1960). Since then, there has been a lack of consensus in diagnostic criteria, because of the varying presentations of NMS, low incidence rates, and limited research.

Three common diagnostic paradigms for characterizing NMS have been published (American Psychiatric Association; Levenson 1985; Caroff and Mann 1993). Core features of NMS are hyperpyrexia and rigidity (Levenson 1985; Caroff and Mann 1993). Other typical symptoms include autonomic instability, mental status changes, and elevated laboratory markers (creatinine kinase [CK], liver function tests [LFTs] and white blood cell count [WBC]).

Serotonin syndrome (SS) is a similar life-threatening symptom cluster associated with serotonin-enhancing agents (Boyer and Shannon 2005). Differentiating NMS from SS can be difficult, because of their similar presentations. They typically both present with altered mental status, rigidity, hyperpyrexia, and autonomic instability. When multiple medications are involved impacting both serotonin and dopamine pathways, the diagnosis can be more difficult to elucidate (Perry 2012).

Pediatric cases of NMS and SS continue to be rare. The first literature review of NMS in children and adolescents examined 77 cases related to use of typical antipsychotics (Silva et al. 1999). There have been no literature reviews of pediatric SS cases, but there continue to be rare case reports published (Godinho et al. 2002; Huynh et al. 2013).

We present a complex case of pediatric NMS involving the use of risperidone, paroxetine, valproic acid, methylphenidate extended release (ER) and pramipexole.

Case Report

History of present illness

A 12-year-old Caucasian male was brought to the pediatric emergency room for altered mental status and abnormal movements of 2 days' duration. Two days prior to presentation, he had had flailing arm movements with repetitive right arm cycling in front of his face. He had developed a wide-based gait with his upper

body described as leaning forward with his head down. He was taken to a community hospital emergency room where he received 1 mg of lorazepam. He was discharged back home with reported improved symptoms. The next day his mental status had worsened, with increasing confusion, word-finding difficulties, rigid upper body, impaired gait, and circular arm movements. He was then brought to the local academic medical emergency services.

Medications on admission were paroxetine 40 mg q. a.m., risperidone 0.5 mg q. a.m. and 1 mg at bedtime, methylphenidate ER 36 mg q. a.m., valproic acid 375 mg q. a.m. and 500 mg at bedtime, pramipexole 0.125 mg at bedtime, and melatonin 5 mg at bedtime as needed for sleep. He had been on risperidone for 2 months, and the dose had been increased from 0.5 mg b.i.d. to 0.5 mg q. a.m. and 1 mg at bedtime within the past month. He had no history of taking other antipsychotics prior to risperidone. He had been taking paroxetine for 14 months and pramipexole for 9 months.

On initial examination, he was noted to be diaphoretic with sialorrhea. His speech was slurred, and his mental status was noted to be confused, sleepy, and not oriented. Vital signs ranged from blood pressure of 105–117/57–80 mm hg, temperature 35.2–38.5°C, pulse 87–190 bpm, and respiration rate 22–30. Approximately 1 hour later, he developed tremor and became increasingly tachypnic (respiration rate in the 30s) and tachycardic (pulse 180–190 bpm). He grew agitated, unresponsive, and rigid, with decerebrate and opisthotonos posturing and dysphagia. He was described to have whole body tremors and shivering. Myoclonus was not specifically elicited on any examination, but was described by one emergency room note. Patellar reflexes could not be obtained because of the patient's rigidity, but all other reflexes were noted as 2+ or 3+. Plantar reflexes were downward. Pupils were noted as 4 mm and reactive. The patient received 2 mg of lorazepam IV three times without effect. He was intubated and transferred to the pediatric intensive care unit. Poison control was called and they proposed possible SS caused by an interaction between paroxetine and pramipexole. The patient was started on cyproheptadine 8 mg every 6 hours as well as ceftriaxone, vancomycin, and acyclovir empirically. All outpatient medications were discontinued. Initial differential diagnoses by pediatric and neurology teams included seizure, SS, and NMS, with most involved teams giving a diagnosis of SS.

Initial imaging studies revealed an unremarkable noncontrast head CT, brain and brainstem MRI, and chest radiograph. Electroencephalogram (EEG) showed excessive, very slow high amplitude

delta waves consistent with moderate severe diffuse disturbance of cerebral function. There was no epileptiform or ictal activity. Electrocardiogram (ECG) showed normal sinus rhythm with corrected QT of 443. KUB was significant for severe constipation requiring enema treatment to resolve. Laboratory analyses revealed elevated CK of 664 IU/mL and ammonia level of 70 μ g/mL. Complete blood count, electrolytes, and renal and liver functions were within normal limits. Ferritin was 51 ng/mL. Valproic acid level was 91 mcg/mL. Urine analysis and urine drug screen were negative. Toxicology was negative for ethanol, acetaminophen, and salicylates. Lumbar puncture was benign and all cultures were negative. The patient's mental status and physical symptoms improved in 5 days after symptom onset.

A psychiatrist was consulted and gave a diagnosis of NMS, because of the timing of onset; recent starting and increase of risperidone; and lack of myoclonus, mydriasis, and gastrointestinal symptoms. The patient's mother maintained that he had had a positive response to risperidone, and expressed concern about his psychiatric symptoms returning if he was not taking the medication. After a discussion with the pediatric team and the mother, risperidone was re-challenged at a dose of 0.5 mg on day 5 of hospitalization. Within 9 hours, the patient became diaphoretic, tachycardic, tremulous, rigid, and anxious. CK increased from 256 IU/mL to 309 IU/mL. Risperidone was discontinued, and the patient's clinical course again improved. He was started on lithium for a diagnosis of bipolar affective disorder.

Psychiatric history

The patient had been diagnosed with posttraumatic stress disorder (PTSD) age 5, and with PTSD and major depression at age 9; at age 10, his diagnosis was changed to bipolar disorder not otherwise specified, and he was then also diagnosed with generalized anxiety disorder at age 11.

He had multiple psychotropic trials including dextroamphetamine/amphetamine, lisdexamfetamine, methylphenidate immediate release (IR), guanfacine, clonidine, oxcarbazepine, bupropion, fluoxetine, sertraline, atomoxetine, buspirone, trazodone, clonazepam, and lorazepam.

Medical history

He had a history of partial complex seizures at age 18 months. He was started on valproic acid which was stopped when he was 8 years of age. He had a seizure after being placed on bupropion at age 10. Bupropion was immediately discontinued, and he was restarted on valproic acid for seizure control. He also had a history of restless leg syndrome (RLS), and iron-deficient anemia.

Discussion

Risk factors for NMS include polypharmacy, drug interactions that can increase antipsychotic levels, recent medications, and prior episodes of extrapyramidal symptoms (EPS) (Croarkin et al. 2008). Use of a selective serotonin reuptake inhibitor (SSRI) and antipsychotic concomitantly has been associated with increased risk of NMS (Stevens 2008). *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (DSM-5) lists potential risk factors as prior episodes of NMS, higher doses of antipsychotics and rapid dose increases, agitation, exhaustion, dehydration, and iron deficiency (American Psychiatric Association 2013). He had multiple drugs impacting dopamine and was taking both an SSRI and antipsychotic. He had a history of iron deficiency and may have been

predisposed to dehydration as he was living in a dry desert. Some risk factors were not present. His dose of risperidone was not high, nor had it recently been changed with a rapid dose increase. There were no known prior episodes of EPS.

This case demonstrates the increased risk of NMS when multiple medications impacting dopamine pathways are utilized. Medications in this patient's regimen were both directly and indirectly reducing dopamine. Risperidone causes direct antagonism of the dopamine D2 receptor. Paroxetine can reduce dopamine through both pharmacodynamic and pharmacokinetic mechanisms. Paroxetine can also reduce dopamine by inhibition of risperidone metabolism via the 2D6 pathway, increasing risperidone blood levels and D2 receptor occupancy (Caley 1997; Stevens 2008).

The patient was also taking multiple medications serving to increase dopamine, including pramipexole and methylphenidate. Dopamine agonist withdrawal has been associated with NMS (Simpson and Davis 1984; Friedman et al. 1985; Wu et al. 2011). The sudden discontinuation of these medications may have exacerbated the clinical presentation of NMS and/or time to recovery.

Because of evidence on KUB of severe constipation, it is possible that blood levels of both paroxetine and risperidone were elevated, thus increasing the risk of both SS and NMS.

Diagnosis of NMS is often difficult, given the varying diagnostic paradigms and varying presentations of NMS, particularly within the pediatric population. In this case, there was initial diagnostic uncertainty of SS versus NMS and the patient was presumptively treated for SS. Presenting factors suggestive for SS were hyperkinetic, stereotypic movements of the arms; tremor; and use of paroxetine. Although the patient's CK level was four times the upper limit of normal, it was lower than what is typically seen in NMS. Leukocytosis was also absent. This case presented with inconsistently reported variables for SS, including clonus and hyperreflexia. Myoclonus was briefly documented in the emergency room, but at no other time was myoclonus elicited on examination. The patient was noted to have varying reflex responses ranging from absent to mild hyperreflexia. Factors less suggestive of SS included timing of onset (maintained on same dose of paroxetine for 1 year), time to symptom resolution (5 days), inconsistent report of hyperreflexia and myoclonus, and lack of mydriasis or diarrhea. Moreover, when the patient was re-challenged with risperidone, his symptoms returned.

Some have considered that SS and NMS may both occur along a spectrum of the same disorder (Steele et al. 2011). NMS is thought to be an idiosyncratic drug reaction that is not dose related. SS is thought to be dose related, with the likelihood of SS occurring increasing on higher doses of serotonergic agents. This patient was on 40 mg of paroxetine, but on no other highly serotonergic agents. It may be that the physical examination findings showed evidence consistent with both NMS and SS, because he was experiencing symptoms of both. There have been several case reports of NMS and SS overlapping in patients on both an antipsychotic and an SSRI. Some have proposed "neurotoxic syndrome" when elements of both NMS and SS are present (Reeves et al. 2002; Kim et al. 2007).

Conclusion

This case illustrates the difficulties of psychotropic polypharmacy in the pediatric population, as well as the importance of not prescribing without knowing which other medications a patient is taking. Pramipexole had been prescribed by a sleep specialist who had not noted which other medications the patient was taking.

This highlights the importance of increased collaboration between prescribing providers to help reduce prescribing medications with potentially complicated or life-threatening drug–drug interactions.

There is a focus in the literature on checking for EPS, avoiding high doses and rapid increases, and checking for previous episodes of NMS when prescribing antipsychotics for a pediatric population. We would further emphasize recommendations to carefully monitor for iron deficiency anemia, constipation, and dehydration in pediatric populations taking antipsychotics, particularly when polypharmacy is needed to maintain psychiatric stability. We would also recommend further exploration of the overlap between NMS and SS, as they share many common features, and as prescribing medications that have effects on both dopamine and serotonin simultaneously is an increasingly common practice.

Disclosures

No competing financial interests exist.

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