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Case Report

Neuroleptic Malignant Syndrome in a Patient with Autism Spectrum Disorder: Case Report

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Abstract

Neuroleptic Malignant Syndrome (NMS) and Malignant Catatonia (MC) are conditions with significant overlap and are classically characterized by autonomic dysfunction, rigidity, bradyreflexia, posturing, lead-pipe rigidity in the former and waxy flexibility in the latter, stereotyping, an increase in creatinine kinase, and/or leukocytosis. Onset after inciting factor ranges from days to weeks, as does resolution with appropriate treatment. The overlap in symptomatology with Autism spectrum disorder (ASD) presents a formidable diagnostic challenge in a situation that must be parsed out with alacrity and accuracy. An 18-year-old male with a history of ASD, developmental delay with limited verbal use (functional age of approximately 5 years), and intermittent explosive disorder initially presented to an outside inpatient psychiatry hospital for worsening agitation that had spanned several weeks. At the outside facility trazodone, haloperidol, and clonazepam were added to his usual home regimen of valproic acid and escitalopram. Over the course of the next two weeks, he developed lethargy, tachycardia, and hypertensive emergency at which point he was transferred to our medical center's Emergency Department. Due to concern over infection vs

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NMS/MC, an initial treatment plan consisted of: strict avoidance of all antipsychotics, scheduled acetaminophen for antipyretic care, 100 cc/hr IV fluids for rhabdomyolysis, a respiratory PCR panel, blood cultures, lorazepam 2 mg IV q6h, valproic acid 250 mg IV BID PRN for agitation, and discontinuation of patient's home escitalopram. As patient was scoring positively for catatonia per Bush-Francis rating scale with scores of up to 20 and notable for marked tremulousness, myoclonic movements, rigidity with negativism, waxy flexibility, gegenhalten, and fever, the psychiatry service recommended starting a bromocriptine trial of 2.5 mg PO every 8 hours due to worry for progression to NMS/MC due to the antipsychotics he had received at the outside psychiatric facility. After down-titrating the bromocriptine dose as his symptoms resolved and up-titrating to doses as high as 7.5 mg every 6 hours when fever and concern for lead-pipe rigidity developed over a week after his symptoms had initially resolved, after nearly a month our patient was able to successfully be titrated down to a home regimen of lorazepam 1 mg at bedtime for the next 6 months. What made this case particularly unique (other than NMS/MC and ASD sharing many characteristics) were the many logistical hurdles that had to be navigated: first, our institution does not have an in-house Medicine-Psychiatry floor or electroconvulsive therapy (ECT), the definitive treatment for NMS/MC; second, there were neither adult nor pediatric inpatient Medicine-Psychiatry facilities in our state equipped with ECT that were willing to accept our patient as a transfer due to his developmental and physiological age, respectively. This case demonstrates the significant overlap in NMS/MC and ASD, illustrates the importance of recognizing these parallels so that appropriate treatment may be initiated (e.g., knowing one's patient very well before making the decision to treat catatonia presenting as agitation in ASD with antipsychotics), and brings to light the stark reality of logistical challenges in medicine. Our patient's symptoms resolved with bromocriptine and lorazepam and he tolerated the taper without complications.

Keywords
Autism spectrum disorder; Neuroleptic Malignant Syndrome (NMS); malignant catatonia; catatonia; clinical case report; adverse event; differential diagnosis; treatment; antipsychotics; benzodiazepines; electroconvulsive therapy; consultation liaison psychiatry

1. Introduction

In order to ensure our readers are able to fully engage with our case report; understand the epidemiology as well as recognize the overlap and complexity in differentiating between and treating the symptoms of Autism spectrum disorder, catatonia, neuroleptic malignant syndrome; and appreciate the formidable diagnostic challenge and logistical hurdles our team faced in treating our patient – we felt it would be helpful to provide a brief overview on the aforementioned topics before delving into a dense and nuance-filled case presentation.

1.1 Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent impairments in social communication and social interaction as well as restricted and repetitive patterns of behavior, interests, or activities. ASD is typically diagnosed in early childhood and affects individuals across their lifespan. The exact causes of ASD are still unclear, but research suggests that it likely arises from a combination of genetic, environmental, and neurobiological factors [1, 2]. There is no known cure for ASD, but early intervention and behavioral therapies have been shown to be effective in improving outcomes for individuals with this disorder. The diagnosis of ASD is based on clinical criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [3].

To meet a diagnosis for ASD, one must demonstrate persistent deficits in areas of social communication and interaction, such as social-emotional reciprocity; nonverbal communicative behaviors such as body language; and developing, maintaining, and understanding relationships. Further, one must demonstrate at least two kinds of restricted, repetitive behaviors or interests, such as stereotyped or repetitive movements or speech, insistence on sameness, highly restricted and fixed interests that are abnormal in intensity or focus, and hyper- or hypo-reactivity to sensory input. Further, one's symptoms must have both been present in the early developmental period and cause clinically significant impairment in social, occupational, or other important areas of current functioning. Finally, these disturbances are not better explained by intellectual disability or global developmental delay, although these conditions can frequently be comorbid [3].

Several studies have contributed to our understanding of ASD, of which the Centers for Disease Control (CDC) estimates that 1 in 36 (2.8%) 8-year-old children have been identified with autism spectrum disorder (ASD), indicating that ASD is a relatively common condition [4, 5]. Research has also shown that the brain of individuals with ASD may differ in terms of its structure and function, with some studies suggesting that there may be disruptions in the development and connectivity of certain neural networks [6].

Other studies have focused on identifying potential risk factors for ASD. For instance, a meta-analysis by Gardener and colleagues found that advanced parental age, maternal prenatal medication use, and preterm birth were all associated with an increased risk of ASD [1]. Other research has suggested that environmental factors such as exposure to toxins, infectious agents, and nutrition status during prenatal or early postnatal development may also play a role in the development of ASD [2, 7].

1.2 Pharmacologic Treatments for Autism Spectrum Disorder

In terms of treatment, there are no known medications that are able to treat ASD itself in the conventional sense. However, there are numerous therapeutic treatments available to manage symptoms, such as maladaptive problems and behaviors (e.g., irritability and aggression), ADHD-like symptoms (e.g., motor hyperactivity and inattention), repetitive and restrictive behaviors as well as non-pharmacological therapies for social-emotional deficiencies (e.g., applied behavior analysis, which involves the use of positive reinforcement to teach new skills and behaviors [8], social skills training, and speech therapy [9]).

When considering only FDA approved drugs, antipsychotics are the strongest evidence-based treatment for maladaptive behaviors in individuals with Autism Spectrum Disorder (ASD), with

risperidone and aripiprazole being among the most studied and most commonly used [10-13]. Haloperidol has been shown to be inferior to Risperidone in a double-blinded, prospective study with 30 participants and has also been linked to higher rates of extrapyramidal symptoms such as dystonia and dyskinesias [14-16]. Olanzapine, quetiapine, ziprasidone, and clozapine have weaker evidence of effectiveness in treating maladaptive behaviors in ASD and are associated with side effects such as weight gain and sedation [10].

For inattention and hyperactivity, methylphenidate has stronger evidence of efficacy, although its efficacy in children with ASD is lower (about 50%, as determined by teacher-rated hyperactivity subscale of the Aberrant Behavior Checklist) than in those with ADHD alone [17-19]. Atomoxetine has strong evidence for a mild benefit, with moderate improvement in ADHD symptoms but not clinical global impression scores compared to placebo [20]. Other amphetamines have poor data, but are frequently used in practice, while Alpha-2-Agonists (i.e., clonidine and guanfacine) have a mild benefit but considerable side effects. Guanfacine was found to be helpful in reducing behavioral symptoms such as hyperactivity, impulsiveness, and distractibility but may induce sedation, constipation, irritability, and aggression [21]. Clonidine was shown to decrease irritability, stereotypy, hyperactivity, inappropriate speech, and oppositional behavior but may cause hypotension [22].

For repetitive behaviors and rigidity, risperidone is the most strongly evidence-based treatment and is approved by the FDA for the treatment of irritability presenting with aggression, tantrums, or deliberate self-injury in children with ASD age 5 and up [10, 23]. Buspirone has also shown significant effects on restrictive/repetitive behavior in a low-dose randomized controlled trial of around 166 participants, but it has only been studied in 2-6-year-olds [24]. Weak evidence suggests the use of SSRIs and TCAs, mostly for their efficacy with behavior control in obsessive-compulsive disorder [25], although no consistent benefit has been shown despite several randomized controlled trials. The role of SSRIs in anxiety specifically has not been studied. Valproate has only been studied in one small randomized controlled trial.

1.3 Autism Spectrum Disorder and Catatonia

Catatonia can be understood as a spectrum, with less severe variations at one extreme (simple, benign catatonia) and more intense variations, entailing hyperthermia and autonomic instability at the other end (malignant catatonia). Catatonia is a behavioral motor dysregulation syndrome marked by an inability to move normally despite full physical capacity, which can occur in the context of many underlying psychiatric and general medical disorders. The DSM-5 deems catatonia diagnosable when 3 or more of the following symptoms are present: mutism, stupor, catalepsy, waxy flexibility, negativism, posturing, mannerism, stereotypy, unresponsive agitation, grimacing, echolalia, and echopraxia, and when is classified as associated with another mental disorder, due to another medical condition, or unspecified catatonia. Malignant catatonia (i.e., “lethal catatonia”) is an acute onset life-threatening subtype of catatonia that is characterized by fever, autonomic instability, delirium, and rigidity [3]. The mortality for malignant catatonia has fallen from an estimated 75% mortality rate prior to the introduction of antipsychotic medications to a now-estimated 10% mortality rate [26].

Catatonic features can appear in ASD, and there can be overlap in symptoms across catatonia and ASD. There has been increasing interest in the overlap of catatonia and ASD, as symptoms of

social indifference, mannerisms, and echolalia are common to both catatonia and ASD. A diagnosis of catatonia in ASD might result in difficulties in its identification due to the overlap in symptoms between these two conditions.

A systematic review by Vaquerizo-Serrano et. Al. including 12 studies and comprising 969 individuals showed that 20.2% of ASD individuals had features of catatonia. Of those ASD individuals with catatonic features, 85% had motor disturbances. In terms of catatonic symptomatology: 29.0% to 100% of those with ASD had impaired speech; 69.5 to 85.0% displayed lack of cooperation and negativism; 62.0 to 75.2% had agitation uninfluenced by external stimuli; 62.0 to 70.3% displayed sign of aggression; 63.3% had posturing; 47.5 to 61.3% had echolalia; 54.0-55.6% had grimacing; 19.4 to 61.1% had stereotypies and other repetitive movements; 30% displayed odd social communication and difficulty in identifying emotions or experiences; and 50% of the ASD individuals with catatonic features were passive in social interactions [27].

This meta-analysis found that 10.4% (5.8-18.0 95% CI) of individuals with ASD have catatonia. They found that motor disturbances were common in ASD subjects with catatonia and no differences in comorbidity. Several treatments have been used in ASD with catatonic features, including benzodiazepines, antipsychotics, and electroconvulsive therapy (ECT). The findings of the systematic review showed that ECT might help manage catatonic symptoms. The authors noted that benzodiazepines were used in 55.6-95.5% individuals [27].

Benzodiazepines are the most extensively studied treatment for catatonia, with reports of good response and good tolerability. There is support for the efficacy of benzodiazepines, especially lorazepam, in mild catatonia in typically-developing individuals associated with affective symptoms when treatment is initiated quickly after symptom onset. In the case of benzodiazepine use in catatonia in autism spectrum disorder, however, benzodiazepines were not found to demonstrate a clear benefit in the resolution of catatonia. Reasons for discontinuation were found to be due to lack of improvement (33.3%), due to only partial responses (38.1%), due to sedation (9.5%), and due to behavioral worsening (9.5%). Four patients who failed lorazepam therapy responded to ECT, and maintenance electroconvulsive therapy was necessary for sustained symptom remission. Thus, the authors concluded that catatonic patients with ASD may respond less robustly to benzodiazepines and postulate that this might be due to catatonia in ASD having distinctive underlying deficits (i.e., GABA dysfunction appears to be a common biological substrate in both) that might make catatonia less responsive to benzodiazepines. Low doses of atypical antipsychotics are known to have weak GABA-nergic activity and serotonin antagonism that could stimulate dopamine release in the prefrontal cortex and thus alleviate catatonic symptoms, and the aforementioned meta-analysis found that antipsychotics were used in anywhere from 27% to 100% of individuals depending on the institution conducting the study; thus, there seems to be a wide variation in practice [27].

Although there have been several case reports of successful treatment with atypical antipsychotics, some authors recommend avoiding antipsychotics altogether in catatonic patients due to the risk of worsening the condition or even inducing malignant catatonia (especially with the use of first-generation antipsychotics). The addition of antipsychotics differs from how catatonia is usually treated (i.e., benzodiazepines), and thus many experts recommend against treating catatonia with antipsychotics unless there is an underlying psychotic disorder.

Finally, as far as treatments for catatonia are concerned, is electroconvulsive therapy (ECT). Vaquerizo-Serrano et al found that ECT was used in 22 individuals out of 1,534 [27]. The mechanism by which ECT is thought to treat catatonia is by increasing the GABA-nergic activity in the brain and

is reported to be 80-100% effective in reversing symptoms [28]. The use of ECT is recommended in patients who fail to respond to medical treatments, including a trial of lorazepam or another benzodiazepine, and maintenance ECT is important for sustained symptom remission [29]. The induction of seizures to provide rapid recovery was reported as far back as the late 1930s, far before larger observational studies described the effectiveness of ECT in treating catatonia [30]. There are case reports of ECT effectively treating catatonia caused by myocardial infarction, lupus, encephalomyelitis, multiple sclerosis, and other complex medical conditions [30]. Although ECT is considered first line treatment for malignant catatonia, it unfortunately is not universally available.

The British Association for Psychopharmacology recently published a set of evidence-based consensus regarding guidelines for managing catatonia, including guidelines for treating malignant catatonia and NMS, that was formulated by a group of international experts from a wide range of disciplines. It delved into clinical assessments of catatonia, treatment approaches (i.e., first-line, treatment, non-response, complications), alternative therapies (e.g., NMDA receptor antagonists, dopamine receptor antagonists and partial agonists, transcranial magnetic stimulation, etc.), subtypes of catatonia and related conditions (periodic catatonia, malignant catatonia, NMS, and antipsychotic-induced catatonia), as well as laid out some considerations for special groups (e.g., children, the geriatric population, and those with ASD). Regarding recommendations they agreed upon specifically for catatonia in those with ASD, they recommended mild cases of catatonia to be treated with psychological interventions and/or lorazepam with moderate and severe cases warranting benzodiazepines in escalating dosages and/or bilateral ECT [26].

2. Case Presentation

2.1 Outside Psychiatric Facility Hospitalization Leading Up to ED Transfer

A 18-year-old male with history of Autism spectrum disorder (ASD), developmental delay with limited verbal use (functional age of approximately 5 years), and intermittent explosive disorder initially presented to an outside inpatient psychiatry hospital for worsening agitation and aggression spanning several weeks. At school, patient was attacking staff, biting classmates, and was displaying behaviors indicating increasing impulsivity. At home, his aggressive behavior reportedly got so bad that he bit his mother while she was driving, prompting a car accident. Thus, his parents brought him to an inpatient psychiatric hospital, where he was initially quite agitated: pacing the halls, biting staff and other patients, and requiring multiple psychotropic PRN medications including trazodone (50 mg), haloperidol (5 mg BID), and clonazepam (2 mg BID). Over the next few days, he became less responsive, no longer pacing or requiring PRNs for agitation. However, about a week after the initiation of the aforementioned antipsychotics, he developed lethargy with unresponsive episodes, tachycardia, and hypertensive emergency at which point he was transferred to our medical center's Emergency Department (ED).

2.2 Presentation in Emergency Department

While in ED, patient was febrile to 101.1°F, tachycardic to 130 beats/minute, hypertensive at 159/90, and was found to have a creatinine kinase (CK) elevated to 771, a white blood cell count elevated to 11.1, and a D-Dimer elevated to 1079. A CT-head and CT-PE were unremarkable. The Psychiatry Consult-Liaison service was consulted for a concern for serotonin syndrome. Our patient

was interviewed with parents at bedside. On interview, our patient did not speak but would intermittently respond to direction (he could open his eyes at interviewer's request and looked to parents several times throughout the interview). Per his parents at bedside, he was diagnosed with ASD in 2004 and had been stable on valproic acid 250 mg BID and Lexapro 7 mg for many years. He had never been so agitated his whole life as he had been the past two months, nor had he ever had similar episodes of lethargy or decreased interactiveness previous to his recent admission. His parents thought his worsening agitation might have been due to recent weight gain making his medications less effective. They also shared that he had been trialed on many different medications but had side effects from many of them, including blepharospasm on aripiprazole and weight gain on risperidone. He had not had any recent medication changes prior to this most recent hospitalization. At baseline, he is able to speak, read, and write at the level of a 5-year-old and has mild rigidity of the upper extremities. He regularly follows with an outpatient medical speech-language pathologist and occupational therapy. On physical examination, patient seemed mostly nonresponsive, intermittently groaning. He was found to be tachycardic with a II/IV systolic crescendo murmur. He had multiple areas of ecchymosis over the thighs and bilateral upper extremities. He was rigid in the upper extremities, and he was regularly flexing his left lower extremity and his left foot was tremoring.

3. Management and Outcome

3.1 Initial Plan and Management

Given his persistent tachycardia, hypertension, rigidity in his upper extremities, elevated CK, and new onset fevers, suspicion was high for iatrogenic conditions such as NMS/malignant catatonia or serotonin syndrome. There was also a concern for sepsis with his fevers. An initial treatment plan was formulated as follows: strict avoidance of all antipsychotics, scheduled acetaminophen for antipyretic care, 100 cc per hour of IV fluids for rhabdomyolysis, respiratory PCR panel, blood cultures, lorazepam 2 mg IV every 6 hours, valproic acid 250 mg IV BID as needed for agitation, discontinuation of patient's home escitalopram, and admission to the Pediatric Intensive Care Unit.

3.2 Revised Plan After the Development of Catatonic Symptoms and Bromocriptine Taper

Two days after admission to the ED, he was scoring positively for catatonia per Bush-Francis rating scale with scores of up to 20 and was notable for marked tremulousness, myoclonic movements, markedly rigid with marked negativism, waxy flexibility, and fever. Thus, due to worry for progression to malignant catatonia/NMS due to the antipsychotics he had received at the outside psychiatric facility, the psychiatry service recommended starting a bromocriptine trial of 2.5 mg PO every 8 hours, which was up-titrated the next day to 5 mg every 8 hours with improvements already seen in patient's symptoms and fever.

After 12 days on bromocriptine, patient's Bush-Francis score had dropped to 2 due to stereotype movement (although even this score was provided with a caveat given some overlap with catatonia symptoms and ASD). His mother reported that patient's symptoms appeared to be improving and that he was acting closer to baseline. Overall, he appeared to be benefiting from the current dose of bromocriptine and current psychotropic regimen given his increased interactiveness, speech, and oral intake.

Two days thereafter, however, as the patient had reached a maximum temperature of 99.5°F overnight, we increased the bromocriptine to 7.5 every 6 hours (along with lorazepam 2 mg q6h, clonidine 0.2 mg oral BID, valproic acid 250 mg oral BID, and melatonin 9 mg at bedtime).

Fortunately, three days after the increased dose of bromocriptine to 7.5 mg, patient had not spiked any more higher temperatures and remained without signs or symptoms of catatonia, both from a physical exam perspective and chart review of autonomic instability. Thus, we began to taper the bromocriptine while continuing to evaluate closely for catatonia symptoms.

From that point on, every few days we reduced the overall daily dosage of bromocriptine by 5 mg (7.5 mg q6h for a total of 30 mg/day to 25 mg/day to 20 mg/day, etc.) until patient was stable on 2.5 mg BID x4 days and finally 2.5 mg once per day x4 days. Lorazepam was planned to be tapered at a rate and dose of 1.5 mg q6h x4 days, then 1 mg q6h x4 days, then 1 mg TID x 4 days, then 1 mg BID x4 days, and finally 1 mg at bedtime x6 months. As before, strict avoidance of all antipsychotics was echoed.

3.3 Outcome and Discharge Planning

On the Pediatrics floor, patient continued to make progress interacting with his caregivers and with various child recreational activities (primarily via his electronic tablet device). Due to some residual symptoms, including deconditioning for which he required continuing Physical Therapy (PT) and Occupational Therapy (OT), he was successfully discharged to Subacute Rehabilitation for maintenance PT/OT.

4. Discussion

This case particularly unique due to both the challenging nature of differentiating between NMS and malignant catatonia in the setting of underlying ASD as well as the logistical hurdles our treatment team had to navigate, of which there were several.

Our patient's increasing agitation in the months leading up to his Emergency Department visit at our facility may have been due to several factors. As his mother suspected, his increasing agitation may have been due to diminishing effectiveness of medications our patient had been taking for years in the setting of significantly increasing weight. Our patient may have happened to be one of the 8-20% of those with ASD who developed catatonia due to increasing GABA-nergic activity or another pathway. He may have just been unhappy with something but unable to adequately communicate it due to his neurodevelopmental delay and subsequently acted out. His agitation may have also been due a combination of several of these factors.

In this case study, our patient's initial presentation was consistent with both NMS and malignant catatonia, both which present with elevated creatine phosphokinase, altered mental status, fever, tachycardia, diaphoresis, and tremors. Although the presence of waxy flexibility swayed the initial diagnosis toward malignant catatonia, given the recent and repeated doses of antipsychotics that were administered at the outside inpatient psychiatric facility in a patient who had otherwise not been exposed to antipsychotics in the past, it is more likely that our patient's sudden-onset lethargy, hypertension, tachycardia, muscle rigidity, and mutism were the result of NMS. This is because a distinguishing factor between the two conditions is that a diagnosis of NMS requires the administration of neuroleptic medication within the past 72 hours, an increased dosage of

neuroleptics, or a sudden withdrawal of dopaminergic agents, whereas malignant catatonia does not require the presence of a neuroleptic drug.

Cessation of dopamine-blocking medications is the most crucial element in enhancing the chances of survival after the onset of NMS [26]. When dopamine-blocking medications are discontinued and appropriate medical support is provided, NMS typically resolves within 10 days. Otherwise, the only other intervention that has been widely agreed upon is cessation of anticholinergic medications to prevent impairment of heat loss through perspiration. Although the following treatments lack consensus – largely due to the rarity of NMS, its inherent self-limiting nature, and the diversity in its onset, progression, and outcomes – there have been several reports of complicated and prolonged courses of NMS successfully treated with benzodiazepines, dopamine agonists, dantrolene, and electroconvulsive therapy (ECT) [26].

Utilization of benzodiazepines in the treatment of mild, early NMS (characterized by mild rigidity, catatonia or confusion, a temperature less than 38°C, and heart rate of less than 100) is reasonable given the proposed overlap between NMS, catatonia, and malignant catatonia, although responses may be transient or non-existent in some instances. Further, dopamine agonists such as bromocriptine and amantadine may alleviate the neurological dopamine deficit, aid in resolving the syndrome, have been linked to reduced mortality rates, and are worth considering for cases of moderate NMS (characterized by moderate rigidity, catatonia or confusion, a temperature between 38 and 40°C, and a heart rate of 100 to 120). Finally, for severe NMS (characterized by severe rigidity, catatonia or coma, a temperature greater than 40°C, and a heart rate of greater than 120), lorazepam, dantrolene, bromocriptine or amantadine, and/or ECT should be considered [26].

As our patient demonstrated moderate NMS, we treated him with lorazepam and bromocriptine (among other supportive measures), both of which he tolerated well. This case report supports the use of these agents in the treatment of moderate NMS.

Regarding the logistical hurdles our team faced, first, our Psychiatry service operates as a consult service as our institution does not have our own Medicine-Psychiatry floor. This meant that there was significant teamwork involved with the primary team (Pediatrics) in helping manage our patient. Secondly, our facility does not offer ETC, the definitive treatment for NMS/MC. As this condition can quickly spiral out of the control of conventional medications' reach (e.g., bromocriptine, amantadine, dantrolene) it was imperative that we found a suitable option for our patient. On that note, thirdly, most inpatient pediatric Medicine-Psychiatry facilities equipped with ECT would not accept our patient due to his age of 18, and most Adult Inpatient Medicine-Psychiatric facilities would not take him due to his developmental age (~5 years old) as he would not have been able to participate in much of the rehabilitation and activities offered and were just all-around not comfortable treating and did not feel well-equipped to treat a "Pediatrics" patient. Thus, our social workers were not able to identify a single facility in our state who would take him as a transfer, which posed a great concern for our patient's safety as he began to spike fevers greater than 99°F, at which point we may have urgently needed to turn to ECT.

This case demonstrates the overlapping symptomatologies in NMS/MC and ASD, illustrates the importance of recognizing this syndrome as crucial so that appropriate therapy and prevention may be put into place (such as knowing one's patient very well before making the decision to treat agitation in ASD with antipsychotics), adds another data point to the currently scarce data pool of moderate NMS successfully treated with lorazepam and bromocriptine given the rare nature of this neurological disorder, and brings to light the stark reality of various facilities' ability and willingness

to take on such a patient for various reasons. We are fortunate that our patient's symptoms resolved with bromocriptine and tolerated the taper well. Future directions include pooling data from multiple centers regarding the treatment of mild, moderate, and severe cases of NMS; the therapies used in each case; and outcomes to better determine the usefulness of and relationship between each of the aforementioned therapies in the treatment of NMS, especially in patients with ASD.

5. Conclusions

There is no treatment of the core symptoms of ASD; however, there are effective pharmacologic treatments which have proven usefulness in controlling some of the associated symptoms of ASD.

ASD and catatonia have many overlapping symptomatologies; thus, it can be challenging to identify when a patient with ASD develops catatonia. It is especially important to know a patient's history, both as far as their typical behaviors as well as the physical manifestations of their ASD, before making a decision on whether to administer antipsychotics for acute agitation or aggression.

While low, there is a risk of developing neuroleptic malignant syndrome or malignant catatonia in patients receiving antipsychotic medication, especially in those presenting with catatonic features. The onset of NMS/MC can occur days to weeks after the inciting factor, and may similarly take days-to-weeks after initiation of appropriate treatment for resolution.

If a patient exhibits signs of NMS/MC such as fever, muscle rigidity, or changes in mental status, all antipsychotic medications should be discontinued immediately. Treatment may include supportive care, such as hydration and cooling measures; the use of medications such as benzodiazepines and bromocriptine, dantrolene, or amantadine; or, as a last resort, ECT to manage symptoms.

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Author Contributions

Stefan Klek - background information, review of literature, primary author. Jonathan Newgren - background information. Angelika Kwak - background information. Eric Casinelli - background information. Tony Tu - background information. Theodote Pontikes - background information. Edwin Meresh - background information, review of literature.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: Comprehensive meta-analysis. Br J Psychiatry. 2009; 195: 7-14.

2. Kalkbrenner AE, Schmidt RJ, Penlesky AC. Environmental chemical exposures and autism spectrum disorders: A review of the epidemiological evidence. Curr Probl Pediatr Adolesc Health Care. 2014; 44: 277-318.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5™ (5th ed.). Washington, DC, US: American Psychiatric Association; 2013.
4. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 Sites, United States, 2014. MMWR Surveill Summ. 2018; 67: 1-23.
5. Centers for Disease Control and Prevention. Autism Prevalence Higher, According to Data from 11 ADDM Communities. Atlanta, GA, US: Centers for Disease Control and Prevention; 2023. Available from: https://www.cdc.gov/media/releases/2023/p0323-autism.html#:~:text=One%20in%2036%20(2.8%25),1%20in%2044%20(2.3%25).
6. Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. Functional and anatomical cortical underconnectivity in autism: Evidence from an FMRI study of an executive function task and corpus callosum morphometry. Cereb Cortex. 2007; 17: 951-961.
7. Schmidt RJ, Niu Q, Eyles DW, Hansen RL, Iosif AM. Neonatal vitamin D status in relation to autism spectrum disorder and developmental delay in the CHARGE case-control study. Autism Res. 2019; 12: 976-988.
8. Lindgren S, Wacker D, Suess A, Schieltz K, Pelzel K, Kopelman T, et al. Telehealth and autism: Treating challenging behavior at lower cost. Pediatrics. 2016; 137: S167- S175.
9. Reichow B, Steiner AM, Volkmar F. Social skills groups for people aged 6 to 21 with autism spectrum disorders (ASD). Campbell Syst Rev. 2012; 8: 1-76.
10. McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med. 2002; 347: 314-321.
11. McVoy M, Findling R. Child and adolescent psychopharmacology update. Psychiatr Clin North Am. 2009; 32: 111-133.
12. Owen R, Sikich L, Marcus RN, Corey Lisle P, Manos G, McQuade RD, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. Pediatrics. 2009; 124: 1533-1540.
13. Marcus RN, Owen R, Kamen L, Manos G, McQuade RD, Carson WH, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. J Am Acad Child Adolesc Psychiatry. 2009; 48: 1110-1119.
14. Anderson LT, Campbell M, Grega DM, Perry R, Small AM, Green WH. Haloperidol in the treatment of infantile autism: Effects on learning and behavioral symptoms. Am J Psychiatry. 1984; 141: 1195-1202.
15. Campbell M, Armenteros JL, Malone RP, Adams PB, Eisenberg ZW, Overall JE. Neuroleptic-related dyskinesias in autistic children: A prospective, longitudinal study. J Am Acad Child Adolesc Psychiatry. 1997; 36: 835-843.
16. Miral S, Gencer O, Inal Emiroglu FN, Baykara B, Baykara A, Dirik E. Risperidone versus haloperidol in children and adolescents with AD: A randomized, controlled, double-blind trial. Eur Child Adolesc Psychiatry. 2008; 17: 1-8.
17. Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry. 2005; 62: 1266-1274.

18. Handen BL, Johnson CR, Lubetsky M. Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. J Autism Dev Disord. 2000; 30: 245-255.
19. Quintana H, Birmaher B, Stedge D, Lennon S, Freed J, Bridge J, et al. Use of methylphenidate in the treatment of children with autistic disorder. J Autism Dev Disord. 1995; 25: 283-294.
20. Harfterkamp M, van de Loo Neus G, Minderaa RB, van der Gaag RJ, Escobar R, Schacht A, et al. A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2012; 51: 733-741.
21. Scahill L, McCracken JT, King BH, Rockhill C, Shah B, Politte L, et al. Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. Am J Psychiatry. 2015; 172: 1197-1206.
22. Fankhauser MP, Karumanchi VC, German ML, Yates A, Karumanchi SD. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. J Clin Psychiatry. 1992; 53: 77-82.
23. Barnard L, Young AH, Pearson J, Geddes J, O'Brien G. A systematic review of the use of atypical antipsychotics in autism. J Psychopharmacol. 2002; 16: 93-101.
24. Chugani DC, Chugani HT, Wiznitzer M, Parikh S, Evans PA, Hansen RL, et al. Efficacy of low-dose buspirone for restricted and repetitive behavior in young children with autism spectrum disorder: A randomized trial. J Pediatr. 2016; 170: 45-53.e4.
25. Soomro GM, Altman D, Rajagopal S, Browne MO. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). Cochrane Database Syst Rev. 2008; 2008: CD001765.
26. Rogers JP, Oldham MA, Fricchione G, Northoff G, Ellen Wilson J, Mann SC, et al. Evidence-based consensus guidelines for the management of catatonia: Recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2023; 37: 327-369.
27. Vaquerizo Serrano J, Salazar De Pablo G, Singh J, Santosh P. Catatonia in autism spectrum disorders: A systematic review and meta-analysis. Eur Psychiatry. 2021; 65: e4.
28. Schumaker A, Klauber R, Aasen M, Padua M, Meresh E. Alcohol withdrawal induced malignant catatonia and response to bromocriptine: Case teport. OBM Neurobiol. 2022; 6: 121.
29. Withane N, Dhossche DM. Electroconvulsive treatment for catatonia in autism spectrum disorders. Child Adolesc Psychiatr Clin N Am. 2019; 28: 101-110.
30. Lloyd JR, Silverman ER, Kugler JL, Cooper JJ. Electroconvulsive therapy for patients with catatonia: Current perspectives. Neuropsychiatr Dis Treat. 2020; 16: 2191-2208.