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Original Article

Neuroleptic Malignant Syndrome in Children and Adolescents on Atypical Antipsychotic Medication: A Review

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Abstract

Objective: Neuroleptic malignant syndrome (NMS) is a severe iatrogenic complication of treatment with antipsychotic medication. The purpose of this report is to examine the published cases of NMS in children and adolescents receiving atypical antipsychotic medication and review early warning symptoms, risk factors, and treatment in this population.

Method: An extensive review of the literature from 1990 to 2008 was conducted via computerized searches (PubMed and Ovid) to identify case reports. Descriptive statistics were employed to describe our findings.

Results: There were 23 episodes in 20 subjects, with ages ranging from 11 to 18 years. Increased creatine phosphokinase (CPK) was the most common finding (100%), followed by fever (78%), tachycardia (74%), rigidity (70%), and altered mental status (61%). The number of NMS symptoms ranged from 1 to 11 (mean 4.7 ± 2.4) and positive laboratory findings ranged from 1 to 4 (2.2 ± 1). The duration of NMS (mean 6.1 ± 6.4 days) was one third of the duration associated with typical antipsychotics. Patients treated with bromocriptine had a shorter duration of illness, whereas the same was not true for those receiving dantrolene. In all cases, the NMS symptoms eventually resolved and there were no reported deaths or permanent sequelae.

Conclusions: NMS is a serious condition. Symptom presentation related to atypical agents differs from that seen with older antipsychotic medications.

Introduction

Neuroleptic malignant syndrome (NMS) is a rare, but potentially fatal complication of treatment with antipsychotic medication and characterized by the development of severe muscle rigidity and hyperthermia, first described by Delay et al. in 1968. According to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) criteria, these required symptoms are accompanied by two (or more) of the following symptoms: Diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, tachycardia, alterations in blood pressure, leukocytosis, and laboratory evidence of muscle injury (e.g., elevated creatine phosphokinase [CPK]).

The investigation of NMS in children lagged considerably behind the work done in adults with the typical antipsychotic agents. In 1999, Silva et al. compiled a review of the literature of 77 cases involving NMS in children and adolescents taking older traditional neuroleptic medication (Silva et al.1999). The authors described a similar course of illness and treatment to that of adults. NMS is thought to be the result of dopamine blockade, both centrally and peripherally, and may represent an aspect of severe extrapyramidal side effects of neuroleptics. The atypical antipsychotics reduce psychosis while decreasing extrapyramidal symptoms (EPS), including NMS (Silva et al. 1999). However, while there has been a multitude of documented cases with NMS in adults treated with atypical agents since the original report of Bonwick et al. (1996) regarding risperidone, less is known about NMS in children who are prescribed atypical antipsychotics. Given that atypical antipsychotics are being increasingly prescribed in the pediatric and adolescent population (Zito et al. 2003), a more global understanding of the relationship between atypical neuroleptics and NMS in this population needs to be explored.

The purpose of this report is to examine the published cases of NMS in children and adolescents receiving atypical antipsychotics and review early warning symptoms, risk factors, and treatments in this population. The review will also attempt to compare NMS cases in children on different

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Table 1. Demographic Information of 23 Episodes of NMS in 20 Children Treated with Atypical Antipsychotics

	Age	*Gender*	*Race*	*Diagnosis*	*Antipsychotic Administered*	*Daily Dosage*	*Adjunctive Medication*	*Time to Onset of Symptoms in Days*	*Duration of Symptoms in Days*	*Number of NMS Symptoms (out of 11 possible)*	*Number of Positive Laboratory Tests (out of 7 possible)*	*Past Antipsychotic Use and Reactions*	*Successful Rechallenge with an Antipsychotic*
Case 1: Mané et al. 2005	17	Male	Caucasian	Schizophrenia	Risperidone	3 mg	none	0.25	3	2	2	none	Clozapine
Case 2: Skarpathiotakis et al. 2005	16	Male	"Iranian background"	Schizophrenia	Clozapine	12.5 mg	Olanzapine 5 mg IM (1 dose)	0.25	unknown	6	1	Loxapine, Olanzapine, Risperidone, Perphenazine, Quetiapine and Fluphenazine	none
Case 3: Chungh et al. 2005	12	Female	Korean	Bipolar disorder	Risperidone	2 mg	Valproic acid 450 mg	29	4	4	4	none	none
Case 3 continued: Same patient, 2nd episode of NMS					Olanzapine	2.5 mg		2	2	1	4		none
Case 3 continued: Same patient, 3rd episode of NMS					Quetiapine	75 mg		3	3	1	4		none
Case 4: Hanft et al. 2004	17	Male	African-American	Acute psychosis	Olanzapine	2.5 bid, 2 mg qhs	Valproic acid 250 mg tid	1	6	6	2	none	Clozapine
Case 5: Abu-Kishk et al. 2004	11	Male	African	Acute psychosis	Clotiapine	40 mg	none	0.25	14	6	3	none	none
Case 5 continued: Same patient, 2nd episode of NMS					Olanzapine	unknown		0.25	3	3	1		none
Case 6: Zalsman et al. 2004	16	Male	Caucasian	Acute psychosis	Risperidone	5 mg	none	10	2	5	1	none	Clozapine
Case 7: Zalsman et al. 2004	17	Male	Caucasian	Acute psychosis	Risperidone	1 mg	Valproic acid 200 mg tid	0	4	5	2	none	Perphenazine

Case 8: Strawn et al. 2008	14	Female	African-American	Bipolar disorder	Olanzapine	15 mg	Topiramate 200 mg bid	56	5	3	1	none	Olanzapine
Case 9: Robb et al. 2000	17	Female	African-American	Bipolar disorder	Risperidone	1 mg	Lithium 600 mg po bid	2	31	2	1	unknown	none
Case 10: Aboraya et al. 2002	18	Male	African-American	Schizophrenia	Olazapine	10 mg	none	5	1	5	2	Risperidone-akathesia and mask-like facies	Quetiapine
Case 11: Sharma et al. 1996	15	Male	Hispanic	Acute psychosis	Risperidone	4 mg	Valproic acid 500 mg, Amantadine 200 mg	3	10	11	2	none	none
Case 12: Spakling et al. 2004	17	Male	African-American	Schizophrenia	Aripiprazole	15 mg	none	3	4	6	2	Quetiapine, Olanzapine, and Ziprasidone	none
Case 13: Leibold et al. 2004	15	Male	Caucasian	Schizoaffective disorder	Ziprasidone	80 mg	Valproic acid 250 mg BID. Buproprion 100 mg bid	56	9	8	2	Risperidone-facial twitching	Olanzapine
Case 14: Berry et al. 2003	16	Male	unknown	Bipolar Disorder	Olanzapine	20 mg	Lithium 1200 mg daily	14	5	4	3	Risperidone-EPS	Risperidone
Case 15: Ghaziuddin et al. 2002	17	Female	"Middle Eastern descent"	acute psychosis	Olanzapine	5 mg then 10 mg (2 doses)	Lorazepam	1	3	8	3	none	none
Case 16: Hammerman et al. 2006	14	Female	Unknown	Depression with psychotic features	Aripiprazole	5 mg	none	2	2	5	1	Olanzapine, Risperidone	none
Case 17: Palakurthi et al. 2007	12	Male	Caucasian	Pervasive developmental disorder	Aripiprazole	10 mg	Methylphenidate 36 mg daily	2	6	2	2	none	none
Case 18: Strawn et al. 2006	18	Male	African-American	Autism and intermittent explosive disorder	Ziprasidone	80 mg	Haloperidol 10 mg IM (two doses), Loraepam 2 mg IM (one dose)	0.5	4	6	2	unknown	none
Case 19: Rais et al. 2008	13	Female	African-American	acute psychosis	Quetiapine	200 mg	none	6	3	3	3	none	none
Case 20: Ty et al. 2001	16	Male	Caucasian	Schizoaffective disorder	Risperidone	unknown	none	4	10	5	3	Haloperidol, Perphenazine	none

atypical antipsychotics to those taking typical antipsychotic medication based on results from the available literature.

Method

An extensive review of the literature from 1990 to 2008 was conducted via computerized searches (PubMed and Ovid). Identified reports were limited to include human subjects, ages 0–18. Parameters included NMS and atypical antipsychotics. Case reports were identified and reviewed, and all reference sections were checked for additional cases. Authors were e-mailed to clarify and fill in missing information in the report.

A preliminary review of the literature served to identify variables that should be included in this review. Of the multiple variables identified, our report includes demographic information such as age, gender, race, clinical psychiatric diagnosis, and medical condition. Medication information includes all medications patients received, dose of medication, and time from initiation of neuroleptics to beginning of NMS. NMS variables include the presence and extent of physical findings, laboratory abnormalities, duration of symptoms, and all treatments, interventions, and outcomes.

Results

Subjects

Table 1 summarizes the demographics of each case report. Nineteen articles identified 23 distinct episodes of NMS reported in 20 subjects (14 males and 6 females). It should be noted that in 2 cases the subject had more than one episode of NMS on different antipsychotic agents. Ages ranged from 11 to 18 years old (mean age 15.4 ± 2.1). The racial composition of these subjects was 40% African American ($n = 8$), 30% Caucasian ($n = 6$), 5% Asian ($n = 1$), 5% Hispanic ($n = 1$), and 10% other ($n = 2$); ethnicity was not listed ($n = 2$) in 10% of the sample. Psychiatric diagnosis for which the patient was being treated included 35% acute psychosis ($n = 7$), 20% schizophrenia ($n = 4$), 20% bipolar disorder ($n = 4$), 10% schizoaffective disorder ($n = 2$), 5% depression with psychotic features ($n = 1$), and 10% pervasive developmental disorder/autism ($n = 2$). Two cases were reported to have preexisting asthma, one of which also had sickle cell trait, but no other preexisting medical conditions were reported.

In addition to taking an atypical antipsychotic medication, 60% of subjects ($n = 12$) were taking adjunctive medication at the time of onset, including medication such as lithium ($n = 1$), one dose of another atypical antipsychotic ($n = 1$), one dose of a typical antipsychotic ($n = 1$), methylphenidate ($n = 1$), topiramate ($n = 1$), lorazepam ($n = 2$), and valproic acid ($n = 5$). Of the patients on valproic acid, 1 patient was concurrently taking buproprion and another patient was also taking amantadine.

Thirty five percent of subjects ($n = 7$) had been treated with antipsychotic medication in the past and 15% of subjects ($n = 3$) had experienced past adverse reactions to antipsychotic medication, all specifically to risperidone. These reactions included akathisia and EPS.

Clinical presentation

Table 2a summarizes the clinical presentation and Table 2b identifies the diagnostic test results of the NMS cases. Each reported case included between 1 and 11 symptoms per patient (mean 4.7 ± 2.4). Fever was present in 78% of cases ($n = 18$) and rigidity was reported in 70% of cases ($n = 16$). In 47.8% of cases ($n = 11$), the subject presented with fever and rigidity together. Tachycardia was another common symptom reported in 74% of cases ($n = 17$). Changes in the level of consciousness were reported in 61% of cases ($n = 14$) (see Table 2a,b).

A range of 1 to 4 positive lab results was reported per case (mean 2.2 ± 1). Increased CPK was the most common finding and was reported in 100% of cases ($n = 20$). CPK levels reached an average of 5550 ± 9755 and ranged from 400 to 40,177 units per liter (U/L) (normal = 27–240 U/L). An elevated white blood cell count was reported in 52% of cases ($n = 12$) of cases in which the lab test was mentioned. There were 3 cases in which the subject had an abnormal electroencephalogram (EEG). Findings included diffuse slowing, indicating mild encephalopathy and abnormalities in the temporal lobe. One case with abnormal computed tomography (CT) findings described decreased activity in the right basal ganglia, left temporal lobe, and both parietal lobes. Positive magnetic resonance imaging (MRI) changes were seen in one subject who experienced 3 separate episodes of NMS (case 3), which showed atrophic changes in the cerebellum. One subject was found to have white cells in the cerebrospinal fluid (CSF).

The time of onset from the initiation of the antipsychotic medication ranged from immediately to 56 days (mean 8.7 ± 16.2 days). The duration of NMS symptoms ranged from 1 to 31 days (mean 6.1 ± 6.4 days).

Medications

The three most common atypical antipsychotics reported in the NMS cases were risperidone ($n = 7$), olanzapine ($n = 7$), and aripiprazole ($n = 3$). Eighty six percent of cases on risperidone ($n = 6$) and 86% of cases on olanzapine ($n = 6$) presented with fever. None of the patients on aripirazole presented with fever, while all patients on aripiprazole ($n = 3$) presented with rigidity and altered mental status. In 57% of cases on risperidone ($n = 4$) and in 43% of cases on olanzapine ($n = 3$), the subjects presented with both fever and rigidity. Seventy one percent of cases on risperidone ($n = 5$) presented with an elevated white blood cell count, including cases in which the test was mentioned. Patients on risperidone had the longest average duration of symptoms (mean 9.14 days) compared to those on olanzapine (mean 3.57 days) and aripiprazole (mean 4.00 days).

Outcome

Table 3 summarizes the different treatments and interventions used once NMS was identified. In 100% of cases ($n = 23$), the antipsychotic was withdrawn and supportive care was implemented. The mean time between first symptom appearance and stopping medication was 0.43 ± 1.12 days. In 19 of the 23 episodes of NMS, the offending agent was discontinued immediately, and in the remaining 4 cases, the range of elapsed time between symptom presentations to medication discontinuation ranged from 6 hours to 4 days. Bromocriptine was administered in 26% of cases ($n = 6$) and dantrolene was administered in 39% of cases ($n = 9$). Benzodiazepines were given in 30% of cases ($n = 7$) and electroconvulsive therapy

Table 2a. Clinical Symptoms of NMS by Antipsychotic

	Average number of total symptoms (out of 11)	*Average duration of symptoms (days)*	*Fever*	*Rigidity*	*Increased heart rate*	*Increased blood pressure*	*Altered mental status*	*Tachypnea*	*Diaphoresis*
Risperidone (7 cases)	4.71	9.14	6 (86%)	5 (71%)	4 (57%)	3 (43%)	5 (71%)	2 (29%)	2 (29%)
Olanzapine (7 cases)	4.29	3.57	6 (86%)	4 (57%)	6 (86%)	4 (57%)	2 (29%)	2 (29%)	1 (14%)
Aripiprazole (3 cases)	4.33	4.00	0 (0%)	3 (100%)	2 (87%)	1 (33%)	3 (100%)	0 (0%)	0 (0%)
Quetiapine (2 cases)	2.00	3.00	2 (100%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)
Ziprasidone (2 cases)	7.00	6.50	2 (100%)	2 (100%)	2 (100%)	0 (0%)	2 (100%)	2 (100%)	2 (100%)
Clozapine (1 case)	6.00	Unknown	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	0 (0%)	1 (100%)
Clotiapine (1 case)	6.00	14.00	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	0 (0%)
Total (23 cases)	4.65	6.09	18 (78%)	16 (70%)	17 (74%)	11 (48%)	14 (61%)	7 (30%)	6 (26%)

Table 2b. Laboratory Test Results in NMS by Antipsychotic

	Average number of positive test results (out of 7)	*Increased CPK*	*Leukocytosis*	*Liver enzymes*	*EEG*	*CT scan*	*MRI*	*CSF*
Risperidone (7 cases)	2.14	7 (100%)	5 (71%)	1 (20%)	1 (50%)	0 (0%)	1 (33%)	0 (0%)
Olanzapine (7 cases)	2.29	7 (100%)	2 (29%)	3 (43%)	2 (67%)	1 (25%)	1 (33%)	0 (0%)
Aripiprazole (3 cases)	1.67	3 (100%)	1 (33%)	1 (33%)	0 (0%)	0 (0%)	0 (NA)	0 (0%)
Quetiapine (2 cases)	2.50	2 (100%)	1 (50%)	1 (50%)	0 (0%)	0 (NA)	1 (50%)	0 (0%)
Ziprasidone (2 cases)	2.00	2 (100%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (NA)	0 (NA)
Clozapine (1 case)	1.00	1 (100%)	0 (0%)	0 (NA)	0 (NA)	0 (NA)	0 (NA)	0 (NA)
Clotiapine (1 case)	3.00	1 (100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Total (23 Cases)	2.13	23 (100%)	12 (52%)	6 (32%)	3 (33%)	1 (10%)	3 (38%)	1 (10%)

Note: Percentages based on cases where test is mentioned.

Abbreviations: NMS = neuroleptic malignant syndrome; CPK = creatine phosphokinase; EEG = electroencephalograph; CT = computed tomography; MRI = magnetic resonance imaging; CSF = ce-cerebrospinal fluid; NA = not applicable.

Table 3. Treatment of NMS

	Supportive treatment	*Antipsychotic withdrawn*	*Bromocriptine*	*Dantrolene*	*Anticholinergic/amantadine*	*Sodium bicarbonate*	*Benzodiazepine*	*ECT*
Frequency	23	23	6	9	4	3	7	4
Percent	100%	100%	26%	39%	17%	13%	30%	17%

Abbreviation: ECT = electroconvulsive therapy.

(ECT) was administered in 17.4% of cases ($n = 4$). In cases where bromocriptine was administered, the mean duration of illness was 5 ± 2.75 days (range from 3 to 10 days), whereas in cases where dantrolene was administered the mean duration of illness was 8.4 ± 8.8 days (range from 2 to 31 days). In the 4 cases where ECT was used, the mean duration of symptoms was 3.25 ± 0.5 days (range from 3 to 4 days), and in the 6 cases where benzodiazepines were given, the mean duration of symptoms was 3.86 ± 2.91 days (range from 1 to 10 days) (see Table 3). The NMS symptoms eventually resolved in all cases, and there were no reported deaths or permanent sequelae. Forty percent of subjects ($n = 8$) were rechallenged successfully with an antipsychotic medication after the episode of NMS resolved. In these cases of rechallenge, all subjects were treated with another atypical antipsychotic, except for one case, which involved perphenazine.

Discussion

This report describes 23 NMS cases in children and adolescents treated with atypical antipsychotics. The subjects appear to present with some similarities and differences in NMS symptoms compared to adult NMS in terms of criteria and course. Only 47.8% of the pediatric aged cases ($n = 11$) presented with both fever and rigidity, which are two required symptoms according to the DSM-IV diagnostic criteria. Only 39% of cases ($n = 9$) met full criteria for NMS by presenting with fever and rigidity together, along with at least two of the other symptoms listed. Elevated CPK was reported in 100% of the reported child and adolescent cases that received atypical antipsychotic medication. It appears that this laboratory finding helped to confirm the diagnosis of NMS in these cases and may represent the hallmark of this illness in childhood presentations. Tachycardia and altered mental status were common symptoms in these case reports, as they are in cases of adult NMS involving typical and atypical antipsychotic medication (Addonizio et al. 1987; Caroff et al. 2000).

The time of onset in these reported cases ranged from immediately to 56 days (mean 8.7 ± 16.2 days), which is consistent with what has been reported in the adult population, which is within 2 weeks and sometimes as early as after a single dose (Addonizio et al. 1987; Farver 2003). NMS developed in these reported cases on relatively small doses of antipsychotic medication, as has been the case with many adult patients (Brown et al. 1999; Farver 2003). Although mortality rates and persistent physical sequelae have been reported in the adult population as a result of NMS (Steingard et al. 1992; Caroff et al. 2000), none of these child and adolescent cases resulted in death or permanent sequelae. Bromocriptine was effective, but dantrolene was not found to shorten the duration of symptoms in this population as it has in cases of adult

Table 4. Comparison of NMS in Children on Typical and Atypical Antipsychotics

	Children on typical antipsychotics	*Children on atypical antipsychotics*
Source of data		
Average age	14.8	15.4
Gender (%M/%F)	49/27	14/6
Average time to onset in days	4.4 ± 9.51	8.7 ± 16.2
Average duration of symptoms in days	17.9 ± 19.97	6.1 ± 6.4
Most common symptoms	Fever (90.3%), rigidity (93.5%), tachycardia (78.3%), altered mental status 72%	Fever (91%), rigidity (70%), tachycardia (74%), altered mental status (61%)
Common laboratory test results	Increased CPK (93.8%), increased WBC (75%)	Increased CPK (100%)
Average time from onset of NMS symptoms to medication discontinuation in days	4.4 ± 9.51	$.43 \pm 1.2$
Treatment	Those treated with bromocriptine had a shorter duration of illness (not found with patients treated with dantrolene).	Those treated with bromocriptine had a shorter duration of illness (not found with patients treated with dantrolene).
Outcome	10.8% (7 cases) resulted in death and 23.1% (15 cases) with physical sequelae. Silva et al. 1999	No deaths or permanent sequelae reported. This study

Abbreviations: NMS = neuroleptic malignant syndrome; M = male; F = female; WBC = white blood cells; CPK = creatine phosphokinase.

typical adult NMS (Addonizio et al. 1987); further investigation is required due to the small number of cases treated with these medications.

Similar to adults, the cases reported predominantly involved male patients (70%, $n = 14$). This may possibly be explained by factors such as a gender difference in age of onset of primary psychotic illness or differences related to rates of exposure to medication. In these cases, the majority of the 6 female patients presented with a primary affective illness such as bipolar disorder or depression (66.7%, $n = 4$), with only two reported cases of acute psychosis. A total of 78.6% of the male cases ($n = 11$) presented with primarily psychotic symptoms, including acute psychosis, schizophrenia, and schizoaffective disorder, with only one case of bipolar disorder and two cases of pervasive developmental delay.

In comparison to NMS cases involving children and adolescents on typical antipsychotic medication, it appears that children and adolescents on atypical antipsychotics have been shown to have an overall similar NMS presentation with some noticeable differences (Table 4). In the Silva et al. review (1999), the children treated with typical antipsychotic medication presented at a similar mean age of 14.8 (as compared to 15.4 years in our sample), yet their sample included 4 subjects below the age of 6, 6 subjects between the ages of 6 and10, and 22 subjects between the ages of 11 and 15. In our review of children treated with atypical antipsychotics, there were no reported cases of young children, despite the increasing number of young children being prescribed atypical antipsychotics (Zito et al. 2003).

In both groups involving cases of NMS in children on typical and atypical antipsychotics, the majority of the subjects were male. Common symptoms of NMS in children treated with typical and atypical antipsychotics included fever, rigidity, tachycardia, and altered mental status. Interestingly, the percentage of children who developed fever and tachycardia with typical and atypical antipsychotics was remarkably similar. An elevated CPK level was a common laboratory finding in both groups (Silva et al. 1999).

The time of onset in children on typical antipsychotics ranged from immediately to 59 days (mean 4.4 ± 9.51) (Silva et al. 1999), while in this sample of children on atypical antipsychotic medication, the average time to onset was nearly double (mean 8.7 ± 16.29 days), with a range from immediately to 56 days. The duration of NMS symptoms in children on typical antipsychotic medication averaged about 18 days (Silva et al. 1999), whereas the duration of symptoms in children on atypicals was approximately one third of this value (mean 6.1 ± 6.46 days). The implication of these observations may be that the cases of NMS induced by atypical agents are less fulminant than those caused by the typical antipsychotic agents.

In the cases involving children on typical antipsychotic medication, there were numerous cases resulting in death or permanent sequelae (Steingard et al. 1992; Silva et al. 1999), in contrast to the patients who received atypical antipsychotic medication, who all had a complete recovery. The timely nature of illness identification and medication discontinuation most likely has played a crucial role in decreasing the mortality of this potentially fatal illness. In a 2001 review by Ty and Rothner, which focuses primarily on traditional agents, the outcomes of pediatric cases of NMS are divided into three epochs. The most recent epoch from 1991 to 1998 shows 0% mortality, compared to 44% (1973 to 1980) and 5.5% (1981 to 1990). This would seem to highlight the fact that increasing awareness and recognition of the syndrome over time has lead to early treatment and prevention of complications and may explain the lack of morbidity and mortality in our sample.

Similar to the atypical antipsychotic cases, the children on typical antipsychotics had a shorter duration of illness when treated with bromocriptine; this was not the case for patients who were treated with dantrolene (Silva et al. 1999). Further research on the effects of bromocriptine compared to dantrolene is warranted due to the small number of patients in our sample treated with these medications. In contrast to children on typical antipsychotics, ECT was shown to be a potentially effective treatment in 4 cases treated with atypical antipsychotic agents. Similar results regarding ECT were reported in the 2008 review of NMS in children on atypical antipsychotics by Croarkin et al. (2008), yet this treatment modality requires further investigation due to the limited number of cases available.

A limitation of this review is the relatively small sample size based on the reported cases in the literature. This may be a true reflection of a lower incidence rate of NMS with atypical antipsychotics as compared to typicals or it may the outcome of early identification and treatments. We were also unable to draw any conclusions on the relative incidence as it relates to specific antipsychotic medications, because our sample size was too small for this analysis.

Conclusions

The notion that NMS in children is associated with presentations encompassing fewer symptoms than are required to meet full criteria of the diagnosis as listed in the DSM-IV should lead to reflection on whether modification of the criteria for children and adolescents should be reconsidered in future DSM revisions. Presentations with fewer symptoms may also be the by-product of earlier identification and intervention of this most serious illness in more recent years (Ty and Rothner 2001). To highlight this point, it should be noted that the average time between the appearance of first symptoms of NMS to medication discontinuation was nearly 10 times longer with the typical antipsychotics (Silva et al. 1999) when compared to the atypical agents examined in this report (4.4 days versus 0.43 days, respectively).

The importance of CPK monitoring in childhood cases highlights the need to make this a first-line diagnostic lab assessment, given that elevated CPK levels were present in all cases in our sample. Elevated CPK may be the diagnostic hallmark of this illness in those children treated with antipsychotic agents in general, because it was also noticed in nearly 94% of child cases treated with typical agents (Silva et al. 1999) as well. When pediatric patients are being treated with an atypical neuroleptic and they develop any of the other symptoms of NMS we have reported, strong consideration should be given to obtaining CPK levels because it is such a prevalent finding associated with NMS in youth.

There may be an interaction between illness and gender in terms of propensity toward developing NMS in children treated with atypical antipsychotics. More specifically, females with affective disorders and males with psychotic disorders were predominant among those who developed NMS

in our sample. Along these very same lines, it is striking that there were no reports of children being treated for aggression secondary to conduct disorder who developed NMS with atypical agents. This may be an artifact of underreporting, but merits further scrutiny.

The main conclusion from this report is that the possibility of a diagnosis of NMS needs to be considered when treating children with atypical antipsychotic medications, in particular in female patients with affective disorders and in males with psychotic disorders. We cannot underestimate the importance of prompt medication discontinuation in potential cases, because it seems to be a vital step in avoiding grave outcomes of this potentially fatal entity.

Disclosures

J.P. Lindenmayer, M.D., has served as a consultant to Lilly and Janssen. Drs. Rachel Neuhut and Raul Silva have no financial ties or conflicts of interest to report.

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