Neuroleptic Malignant Syndrome in Children and Adolescents

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ABSTRACT

Objective: Neuroleptic malignant syndrome (NMS) is a serious iatrogenic condition. This report reviews the world literature to characterize the syndrome and evaluate factors that promote early detection and effective intervention. **Method:** The review identified 77 NMS cases (49 males, 27 females, 1 gender unknown); ages ranged from 0.9 to 18 years (mean 14.8 ± 3.96). Univariate and multiple regression analyses were applied to 38 variables to identify early signs of the disorder, to identify correlates of outcome, and to evaluate treatments. **Results:** The duration of NMS spanned from 1 to 119 days. Nine percent of patients died and 20% resolved with serious sequelae. Patients receiving low-potency neuroleptics had a poorer outcome ($p = .01$). Fever was related to longer duration of illness ($p = .03$). Anticholinergics and bromocriptine were effective and without fatalities, but dantrolene was not useful in this sample of children and adolescents. **Conclusions:** Early detection and appropriate interventions appear important in moderating the course and outcome of NMS. *J. Am. Acad. Child Adolesc. Psychiatry*, 1999, 38(2):187–194. **Key Words:** neuroleptic malignant syndrome, treatment, prognosis.

Delay and Deniker (1968) identified a cluster of adverse effects of antipsychotic medications, including hypertonicity, autonomic instability, fever, and cognitive disturbance, which they named neuroleptic malignant syndrome (NMS). These authors had previously introduced the term *neuroleptics* to describe the diverse class of therapeutic agents with dual actions: (1) the potential for reducing psychosis and (2) the potential for inducing a number of extrapyramidal side effects (EPS). If NMS is an aspect of the EPS reaction to neuroleptics, it may not be totally avoidable when the antipsychotic action is required. However, current views hold that the dual actions of neuroleptics can be dissociated and EPS should be avoided, especially when managing a child's medication. The action of atypical neuroleptics also argues for a dissociation of antipsychotic and EPS mechanisms, although any possible role of these agents in NMS remains to be elucidated with further experience (see Dave, 1995; Singer et al., 1995).

Pearlman (1986) reviewed the NMS literature in the general population and cited incidence rates ranging from 0.5% to 1.4% of individuals exposed to neuroleptics but did not clarify the incidence of NMS in children and adolescents. At least 4 sets of diagnostic criteria of NMS have been published (American Psychiatric Association, 1994; Caroff, 1980; Levenson, 1985; Pope et al., 1986); they differ somewhat in the minimal number of required signs (see Steingard et al., 1992, p. 186), and there is still no consensus on diagnostic requirements. Fever and rigidity are included as cardinal signs in all lists. Seven additional signs and laboratory measures overlap in the 4 criteria sets: elevated creatine phosphokinase (CPK), tachycardia, tachypnea, hypertension, altered consciousness, diaphoresis, and leukocytosis. The frequency of occurrence of these signs differs. Elevated CPK has been identified in up to 97% of assayed children and adults (Addonizio et al., 1987). Tachycardia has been

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reported to occur in more than 75% of cases, a rate similar to that of altered mental state (Steingard et al., 1992). Autonomic disturbances such as blood pressure lability, tachypnea, and diaphoresis are reported less consistently. A case of NMS usually begins with rigidity, which may suggest a connection with EPS, but rigidity is a frequent EPS reaction to neuroleptics, and a specific association with NMS may be spurious. Addonizio et al. (1987) reported that rigidity preceded the fever in 59% of cases and simultaneous onset of rigidity and fever occurred in an additional 23% of cases.

The onset of NMS is often within 2 weeks of neuroleptic initiation (Addonizio et al., 1987), and occasionally after a single dose (Klein et al., 1985). NMS has also occurred after small doses of neuroleptics used for nausea (Brower et al., 1989; Brown et al., 1991). Neither neuroleptic dose nor blood levels have been shown to be causative, and a general mechanism, the rate of increase in neuroleptic blood levels, has been suggested as provocative of NMS (Peterson et al., 1995). This is consistent with the observation that cases occur early in the course of neuroleptic treatment but seem less frequent when steady-state neuroleptic blood levels have been established. Some authors have suggested that high-potency neuroleptics present a greater risk for the development of NMS (Peterson et al., 1995; Susman and Addonizio, 1988).

NMS has a variable course and outcome. Mortality rates in the range of 20% to 22% have been reported (Caroff, 1980; Shalev and Munitz, 1986); in addition to significant mortality, survival of an episode may be associated with persistent physical abnormalities, including renal, hepatic, or neuromuscular impairments (Addonizio et al., 1987; Pearlman, 1986; Steingard et al., 1992). Finally, there is wide variation in the time required for recovery to a premorbid level of functioning.

NMS may have a different course in children. Most of the research has been done with adults, and one of the purposes of this review is to bring together what is known about childhood and adolescent forms in order to renew the attention of child psychiatrists to this condition. Previous reviews have used univariate statistical approaches to examine the efficacy of treatments and outcomes. Peterson et al. (1995) suggested that the "safety and efficacy of these medications for treating youth with NMS remain unclear" (p. 147). Also, Steingard et al. (1992) could not identify common factors associated with cases culminating in death in children or adolescents. The optimal approach would be to establish an experimental design to answer these questions. During a life-threatening illness, however, it is not feasible to experimentally restrict interventions. Alternatively, it is possible to explore these complexities by relying on methods that hold certain critical variables statistically fixed.

This review will explore multiple regression approaches to identify signs associated with outcome and to synthesize information to match the presentation with the course and optimal treatment. Finally, this report will articulate the relevant information that should be included in future case reports of NMS and highlight evidence that prompt and strategic interventions can reduce the mortality and morbidity of this iatrogenic condition.

METHOD

A preliminary review identified variables that should be included—variables germane to the diagnosis of NMS or previously associated with course or outcome. Thirty-eight variables were identified, including the following: demographic—age, gender, race; clinical—psychiatric diagnosis, medical condition, mental retardation; medication—all medications patient received, route and dose of medication, time from initiation of neuroleptics to beginning of NMS; NMS variables—the presence and extent of physical findings, laboratory abnormalities, elapsed time from the first symptom of NMS to its full presentation, time lapse from development of NMS until neuroleptics were discontinued, time from medication discontinuation to the resolution of NMS, and a list of all treatments and interventions.

An extensive review of the literature via computerized literature searches (*Medline* 1966–1998, *PsychInfo* 1984–1998) was conducted. Articles were reviewed and all reference sections were checked for additional cases. All reports of cases aged 18 and younger were reviewed, independently, by 2 board-certified child and adolescent psychiatrists, listing the findings for each of the 38 variables. A consensus meeting was held with a third author where discrepancies were resolved after reviewing the original articles. Three cases were excluded because a consensus diagnosis could not be achieved.

Double data entry was used to minimize input errors. Statistical software used to run these analyses was Systat Version 5.2.1. Most of the reports were not complete with regard to the items that we planned to examine. Exclusion of incomplete reports would have eliminated a large percentage of the reports, and we elected to include as much information as possible. Since uniform reporting was not the rule, we provide sample sizes (n) for each variable.

To evaluate the relative effectiveness of different treatments it was important to create, on a post hoc basis, a measure of severity of the NMS illness. A composite severity score based on the number of NMS signs reported for each case (see Table 1 for the 8 most frequent signs) plus the number of abnormal laboratory findings (see Table 2 for the 8 most common measures) was constructed. These scores are reported in Table 3 as the NMS severity score.

The statistical analysis proceeded from descriptive statistics of clinical signs (Table 1) and abnormal laboratory values (Table 2) and of the various outcome measures. To examine the relations among overlapping clinical signs, which often occurred in clusters, some exploratory hierarchical multiple regression analyses (MRAs) are

TABLE 1
Clinical Presentation of Neuroleptic Malignant Syndrome (NMS)

	Fever	Increased Heart Rate	Blood Pressure Fluctuation	Rigidity	Tremor	Dystonia	Diaphoresis	Incontinence
Frequency[a]	56	47	37	58	19	23	23	9
Total *N*[b]	62	60	57	62	52	54	54	53
Percent	90.3	78.3	64.9	93.5	36.5	42.6	42.5	16.9
Sequelae (*n*)	14	10	10	12	5	5	5	1
Deaths (*n*)	6	5	2	6	2	2	3	1
Duration of NMS[c]								
Median	13.5	14	12.5	12	14	14	12	17
Mean	19.6	18.6	15.1	17.8	22.3	21.1	20.4	18.1
(SD)	(20.8)	(16.2)	(14.2)	(20.7)	(26.3)	(27)	(26.5)	(13.6)

[a] Number of cases in which the symptom was present.
[b] Number of cases in which the symptom was noted as present or absent.
[c] Duration in days.

reported. A similar approach was taken to evaluate the relative efficacy of the multiple treatments that were administered simultaneously. MRAs were performed on variables if there were at least 10 *df* per predictor.

Subjects

The review identified 77 cases (49 males, 27 females, 1 gender unknown) reported in 61 articles (marked by an asterisk in the reference section). Ages ranged from 0.9 to 18 years (mean 14.8 years ± 3.96). Racial composition was as follows: Asian (15.6%), white (11.7%), Hispanic (6.5%%), African-American (3%), other (2.6%), and unlisted (59.8%). The psychiatric diagnoses for which these patients received pharmacotherapy included schizophrenia (24.3%), schizoaffective disorders (5.4%), bipolar disorder (17.6%), and other psychotic diagnosis (23.0%); in 17.6% of cases no psychiatric diagnosis was indicated. Eight patients were described as mentally retarded, another had microcephaly. Premorbid physical health was reported in 62 cases, 38.7% of whom had a medical problem (the most frequent being neurological, $n = 8$).

RESULTS

Pre-NMS Medications

The number of different medications that children were receiving at the onset of NMS, including agents other than neuroleptics, ranged from 1 to 8 (mean 2.9 ± 1.76; $n = 67$). In 61.8% (34/55) of the cases, more than one neuroleptic was administered concurrently. Approximately 72% received a high-potency neuroleptic (including 5.5% who received 3 high-potency agents), while 59.5% received up to 2 different low-potency neuroleptics. Of 65 patients, 17 received an anticholinergic agent, 9 received lithium, 9 received an anxiolytic, 5 were receiving an antidepressant, and 7 were treated with 1 or more anticonvulsants. The duration of treatment with

TABLE 2
Results of Laboratory Tests in Neuroleptic Malignant Syndrome (NMS)

	Increased WBC	Increased CPK	Serum Sodium	Liver Enzymes	EEG	CT Scan	Brain Scan	CSF
Frequency[a]	36	45	4	19	13	3	1	2
Total *N*[b]	48	48	18	30	28	18	6	27
Percent	75.0	93.8	22.2	63.3	46.4	16.7	16.7	7.4
Sequelae (*n*)	7	11	1	5	9	2	0	2
Deaths (*n*)	2	1	2	0	4	0	0	0
Duration of NMS[c]								
Median	14	14	13	14	12	21	14	62.5
Mean	18.5	21	16	27	18.5	27.7	14	62.5
(SD)	(6.8)	(22)	(8.7)	(30)	(18.3)	(25.7)		(79.9)

Note: WBC = white blood cell count; CPK = creatine phosphokinase; EEG = electroencephalograph; CT = computed tomography; CSF = cerebrospinal fluid.
[a] Number of cases in which the test was abnormal.
[b] Number of cases in which the test was performed.
[c] Duration in days.

the offending neuroleptic agent(s) prior to the onset of NMS ranged from 2.5 hours to 168 days (mean 15.5 ± 32.29 days; $n = 64$).

Clinical Presentation

To begin to associate characteristics of the clinical presentation of NMS with interventions and outcomes, 3 tables were constructed. Table 1 summarizes the association between presentation of NMS and outcome. Between 2 and 8 NMS signs were mentioned in the reports for each case. In the table, it can be seen that fever was listed in 56 of the 62 cases in which a patient's temperature was mentioned and rigidity was equally prevalent. In addition, but not included in Table 1, an alteration in consciousness was seen in 72% (44/61), which included coma (19.4% or 11/61).

Course

Time from the appearance of the first symptom of NMS until the full syndrome developed varied from immediately to 18 days (mean 2.8 ± 3.91 days; $n = 53$). Time from the onset of NMS symptoms to the time of medication discontinuation ranged from immediately to 59 days (mean 4.4 ± 9.51 days; $n = 44$); in 33 cases either neuroleptics were not discontinued or their discontinuation was not clearly reported. The time from medication discontinuation to the resolution of the NMS varied from immediately to 61 days (mean 11.8 ± 11.49; $n = 42$). The total duration of NMS ranged from 1 to 119 days (mean 17.9 ± 19.97; $n = 62$).

Outcome

Outcome was clearly delineated in 65 patients; 7 patients died and 15 cases resolved with physical sequelae, including residual rigidity (most commonly reported), brachial plexus palsy, residual dysarthria, liver function abnormalities, atelectasis, increased prolactin levels, and development of other abnormal movements.

In Table 1 it can be seen that fever was associated with poor outcome; 6 of the 7 children who died and 14 of the 15 with physical sequelae were reported to have fever. The relations between abnormal laboratory results and outcome are presented in Table 2. In addition, death was noted in 4 of the 13 cases with abnormal EEG findings, and the other 9 cases suffered persistent sequelae. It appears that EEGs were performed primarily for patients with coma (11/13), which may explain the poor outcome associated with an abnormal EEG. Of the 31 cases for whom confusion was reported, 13 either had a sequela or died. Of the 11 with coma, 5 experienced a similar outcome (4 of whom died). Thus, in the cases reviewed, 18 of the 22 cases with the most severe outcomes presented with an altered level of consciousness.

To generate hypotheses for future work, we examined the characteristics of the 7 cases with fatal outcomes. These children were somewhat younger (mean 12.5 versus 14.8 years), but their most striking characteristic was that the reports describing these cases were published earlier than the average report. Reports of a fatal outcome clustered in years prior to 1976, and no fatalities have been reported since 1986. The duration of illness in patients with fatal outcomes was substantially shorter (mean 7.7 days ± 6.14) than in those who recovered without incident (mean 15.0 ± 14.58 days). It appears that the period of greatest mortal risk is early in the NMS course. The mean duration of illness for patients with physical sequelae was 29.8 days ± 29.93. Cases with sequelae took significantly longer ($p = .007$) to recover from the episode of NMS. Duration of illness provides a useful measure of severity.

Treatment

The number of different interventions and medications per case ranged from 1 to 12 with an average of 3.6. Details concerning treatment interventions are summarized in Table 3. Among other things, it can be seen that the mean severity score for patients who received electroconvulsive therapy (ECT) was less than average, while children who received dantrolene and/or bromocriptine had significantly more signs and symptoms (t test, $t = 5.15$, $p = .001$) than the other children (mean 6.8 ± 2.20 symptoms). Table 3, which includes rates of death and sequelae, shows that dantrolene and L-dopa were each associated with a death, while the other 3 agents were not. The rate of development of sequelae was lowest for anticholinergic agents (17%) and highest for ECT (44%).

Multiple Regression Analysis

We next examined the relations between outcome and the demographic variables (age, ethnicity, and gender). This information could help determine whether these factors should be controlled in further analyses. The demographic variables were unrelated to outcome. With regard to age, in the sample of 77 patients, 4 subjects were below the age of 6 years, 6 were between the

TABLE 3
Treatment Described in the Case Reports of Neuroleptic Malignant Syndrome (NMS)

	Supportive Treatment	Neuroleptics DC'D	Anticholinergics/ Amantadine	Bromocriptine	Dantrolene	L-dopa	ECT
Frequency[a]	35	50	17	18	19	8	9
Total N^b	55	55	48	57	58	58	59
Percent	63.6	90.9	35.4	31.6	32.8	13.8	15.3
Sequelae (*n*)	7	15	3	7	5	3	4
Deaths (*n*)	2	3	0	0	1	1	0
Duration of NMS[c]							
Median	12	12.5	14	13	15	32	19.5
Mean	14.9	19.2	19.9	25.7	21.3	35	24.1
(SD)	(14.8)	(21.6)	(29.3)	(29.5)	(17.9)	(20.3)	(22.2)
NMS severity score							
Median	8	7	7.5	7	7	7	6.5
Mean	7.2	6.8	7.1	7.6	7.6	7.4	5.6
(SD)	(2.1)	(2.1)	(2.5)	(1.3)	(1.4)	(2.1)	(2.1)

Note: DC'D = discontinued; ECT = electroconvulsive therapy.
[a] Number of reports in which the treatment was administered.
[b] Number of reports in which the treatment was mentioned.
[c] Duration in days.

ages of 6 and 10 years, 22 were between the ages of 11 and 15 years, and 45 patients were between 16 and 18 years old; the increased incidence with age probably reflects the lower rate of neuroleptic exposure in younger children.

The first MRA examined outcome in relation to the use of high- and/or low-potency neuroleptics. Previous reports, mainly involving adults, have implicated high-potency agents as presenting greater risk for NMS. Information on the base rate of neuroleptic exposure of children is not available, but in this survey low-potency agents were associated with a poorer outcome ($\beta = .46$, $n = 62$, $p = .01$).

We examined the triad of rigidity, fever, and tachycardia in the group of children who survived the episode ($n = 53$) using duration of illness as the dependent measure ($R^2 = 0.47$, $p < .001$). Fever was related to longer duration of illness ($\beta = .58$, $p = .03$), while neither tachycardia nor rigidity was related to outcome. To examine the association between blood pressure fluctuations and outcome, we performed another hierarchical MRA. In this model ($R^2 = 0.54$, $p < .001$), fever was associated with poor outcome ($\beta = 1.04$, $p < .001$) and blood pressure fluctuations were associated with briefer duration of illness ($\beta = -.48$, $p = .01$). This suggests that blood pressure fluctuations may reflect the influence of compensatory cardiovascular mechanisms.

Another hierarchical MRA was done to examine the association between the different treatments and duration of the NMS episode. The overall model was highly significant ($R^2 = 0.46$, $p < .001$). Many subjects received several medications, and this analysis was designed to separate the unique variance associated with each treatment. Only 53 subjects were available (cases with a fatal outcome were eliminated to permit us to use the duration parameter). The overall model was highly significant; dantrolene and ECT, which have been reported to be effective in adults (Addonizio et al., 1987), were not useful in this sample of children and adolescents. Anticholinergics ($\beta = .27$), bromocriptine ($\beta = .33$), and L-dopa ($\beta = .31$) were all significantly associated with shorter duration of illness.

DISCUSSION

With a few exceptions NMS presents with a form and course in children that is similar to that found in adults. The triad of fever, tachycardia, and rigidity characterizes the presentation in both children and adults. NMS occurred almost twice as frequently in boys. This difference probably reflects the higher base rate of exposure to medication in boys and not a special vulnerability of males to NMS. Although the presentation of these children was similar to that in the broader age range studied by Pearlman (1986) and by Addonizio et al. (1987) in most regards, the children showed a higher rate of dystonia (40.8% versus 29% for all ages) and a lower rate of tremor (32.7% versus 48% for all ages). These differences probably reflect age differences in the rates of these extra-

pyramidal manifestations; dystonia is more common and tremor is less common in these younger patients.

Most importantly, the number of fatal outcomes has dropped sharply for all age groups. Pearlman noted in 1986 that mortality rates had decreased from 22% to 4% over the prior decade. Similarly, we have been unable to locate a report of a fatal outcome in a child or adolescent due to NMS that was published after 1986, whereas prior to that time the mortality rate was 21%. It seems likely that clinicians have become more aware of the dangers of NMS, and some combination of earlier detection, prompt neuroleptic discontinuation, and more aggressive treatment has moderated the fatal course of this iatrogenic disorder. An observation supporting this view is that there are early reports of 5 children for whom neuroleptics were continued after the onset of NMS, 4 of whom died. While the mortality of NMS episodes has decreased with time, the rate at which cases resolve with sequelae has, if anything, increased. Fourteen of the 15 cases with residual physical abnormalities have been reported since 1983, suggesting that survivors of cases that previously might have been fatal are vulnerable to serious organ system damage.

The conservative strategy for the management of anticholinergics remains confusing. Children receiving adjunctive anticholinergic therapy prior to the development of NMS experienced better outcomes if the anticholinergics were discontinued. For children not receiving anticholinergics prior to the development of NMS, initiation of anticholinergics was one of the more effective treatments (see Table 3). It is puzzling that the action of anticholinergics appears to depend on their temporal relationship to the development of NMS. This observation could benefit from further investigation.

Polypharmacy appears to be prevalent in children and adolescents who develop NMS. Despite the fact that many of the children received a number of agents, those receiving low-potency drugs had a poorer outcome. In the group of 15 who developed sequelae, 13 were receiving at least one low-potency agent; similarly, 5 of the 7 children who died were receiving a low-potency agent. This observation may not contradict the suggestion of Pearlman (1986) and Addonizio et al. (1987) that high-potency agents are more likely to provoke NMS because information on the base rates of exposure to these agents is not available.

Because of the seriousness of this condition, it seemed desirable to examine the data closely for clues about underlying mechanisms and optimal interventions. It would be more satisfying if there were a good animal model to pursue some of these leads. A number of indirect observations suggest that NMS is an aspect of the extrapyramidal actions of neuroleptics and reflects processes in the basal ganglia that are set in place by a relative decrease in the access of dopamine to the postsynaptic receptor. Precipitation of NMS does not appear to be related to the dose of neuroleptic but rather follows dose increase and can occur within hours of the first dose or, apparently, after months of maintenance treatment if there is an increase in dose. Of interest is that a syndrome similar to NMS can occur in patients with Parkinson disease if dopaminergic agents are stopped (Friedman et al., 1985; Sechi et al., 1984; Simpson and Davis, 1984). Both the initiation of neuroleptics and the discontinuation of antiparkinson agents are associated with a decrease in the access of dopamine at the postsynaptic receptor. A viable animal model would permit exploration of this observation.

It seems possible that the increased muscle activity associated with the rigidity generates metabolic heat. Consistent with this, increased CPK appeared at a high rate where it was assayed, and elevated CPK was associated with a high rate of sequelae. In the MRA of the triad of NMS signs, when the contributions of fever and tachycardia were controlled, the contribution of rigidity was not related to duration of illness, suggesting that its role in determining outcome may be mediated by its efficiency in provoking fever; it is not clear whether some brainstem disturbance in heat regulation also contributes to the development of NMS since rigidity is common and NMS is rare. The MRAs, which found a positive role for blood pressure fluctuations, suggested that an ability to adapt to cardiovascular stress is positively related to *recovery* from NMS.

The information from the articles we reviewed is limited in obvious and subtle ways. Few of the articles contained uniform information. It might be helpful if the major journals agreed on editorial policies that were more prescriptive as to the material that should be included in case reports. We suggest that the information included in our "Results" section be included in case reports and that the presence of these items be confirmed or denied. Another issue that needs to be acknowledged is that it is unknown whether published cases of NMS are representative.

In the absence of an animal model, it is unlikely that experimental designs can be applied to the study of NMS.

These difficulties increase our dependence on statistical methods to isolate traits that contribute to the course and outcome of NMS. Where we may have violated some of the assumptions of our statistical models, we have been conservative in our clinical recommendations. Until a prospective multisite effort can provide more interpretable results, it seems justified to exploit fragmentary data as fully as possible.

Clinical Implications

In addition to the early identification of the signs and symptoms of NMS, followed by the prompt discontinuation of neuroleptics and management of the anticholinergic status, it is important to provide the medically necessary supportive measures (e.g., fever reduction and intravenous hydration). Our results suggest that bromocriptine be considered a first-line treatment in this condition. As Table 3 suggests, the more favorable outcome with bromocriptine is not an artifact of treating less afflicted children. However, the use of L-dopa, despite being related to shorter illness duration, is also associated with a 50% rate of morbid outcomes. Anticholinergics (initiated after the development of NMS), bromocriptine, and ECT were not associated with a death. It should be remembered that fulminating cases likely elicited heroic efforts that involved multiple treatments, and the poor outcomes of several of the medications listed may result from their use in crisis situations.

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