

Catatonic Variants, Hyperthermic Extrapyramidal Reactions, and Subtypes of Neuroleptic Malignant Syndrome

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Background. This case series study examines the hypothesis that neuroleptic malignant syndrome (NMS) is a heterogeneous condition including catatonic variants and non-catatonic pathological reactions to antipsychotics.

Methods. Fourteen episodes of NMS were prospectively identified. Patients were examined for catatonia during the course of NMS. Close monitoring of catatonia episodes and suspected cases of evolving NMS for possible NMS development provided data on the pre-NMS clinical course. All NMS episodes received benzodiazepines. Episodes with catatonia diagnosed were compared with those without catatonia, noting their presentation, clinical course and responses to treatment.

Results. Concurrent catatonia was diagnosed in 9 episodes. In 6 of them antecedent catatonia progressed to NMS following antipsychotic exposure (NMS of antipsychotic-converted catatonia). In 3 episodes, a parkinsonian-catatonic syndrome with fever and autonomic abnormality developed in reaction to antipsychotics (NMS of antipsychotic-induced catatonia). Catatonia was not diagnosed in 5 during the longitudinal course of NMS. A severe extrapyramidal reaction to antipsychotics with associated delirium preceded all 5 episodes. Seven of the 9 NMS episodes with catatonia and none of the 5 without catatonia showed significant responses to benzodiazepines.

Conclusions. The preliminary findings support the hypothesis that NMS is a heterogeneous condition including catatonic variants and non-catatonic hyperthermic extrapyramidal reactions to antipsychotics, differing in presentation, clinical course, and treatment responses.

Keywords Catatonia, Extrapyramidal reactions, Antipsychotics, Neuroleptic malignant syndrome

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal reaction to antipsychotic medications first described in 1960 in the French literature as “syndrome malin des neuroleptiques” (1). Data on its neurobiology remain inconclusive. Various theoretical concepts of the syndrome have been proposed (2). Delay and Deniker introduced the English translation—neuroleptic malignant syndrome—in 1968, and regarded NMS as an extrapyramidal syndrome with akinesia, hypertonicity and a varying degree of dyskinesia (tremors and dystonia) as the characteristic extrapyramidal symptoms (3). Subsequent studies

of the symptoms of NMS confirm the frequent occurrence of extrapyramidal features in NMS, including leadpipe muscular rigidity, tremors, various focal dystonia, chorea, and myoclonus (4,5). Extrapyramidal symptoms were considered one of the cardinal features of NMS by earlier authors (6,7). It was argued that extrapyramidal side effects (EPS) of antipsychotics and NMS are disorders on the same spectrum with NMS at one end of the spectrum (2,8). The conceptualization of NMS as a subtype of a more generalized spectrum of hyperthermic disorders similar to malignant hyperthermia and lethal catatonia has subsequently gained wide acceptance (9). Muscular rigidity with no specification of its nature has taken over extrapyramidal symptoms as a core feature of NMS, along with fever, autonomic abnormality, and clouding of consciousness (10,11).

Increasing attention has been directed to the close relationship between catatonia and NMS. Catatonia is a neuropsychiatric

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syndrome of diverse etiology defined predominantly by a constellation of motor signs (12). Lethal (malignant) catatonia, a life-threatening condition first described in the pre-neuroleptic literature, simulates NMS (13–15). There have been case reports of NMS with prominent catatonic symptoms responsive to benzodiazepines, often regarded as mild variants of NMS (16–18) resembling the neuroleptic-induced catatonia described in the literature (16,19) but with fever, autonomic abnormality and delirium. Various authors describe the progression of antecedent catatonia into NMS following exposure to antipsychotics (20–22). In their retrospective reviews, Goforth and Carroll (23) and Koch et al. (24) showed that catatonia could be diagnosed in the majority of NMS episodes identified. Cases of residual catatonia following NMS have also been reported (25). Moreover, catatonia and NMS share biochemical findings (21,26) and treatment response (27,28). The close relationship between the two conditions leads to the hypothesis that NMS is a severe variant of catatonia and that NMS and catatonia are one entity sharing similar pathophysiology (20,27,29). It has recently been suggested that NMS be renamed “drug-induced hyperthermic catatonia” with a new set of diagnostic criteria proposed (30).

At variance with this hypothesis, catatonia, though it frequently accompanies NMS (31,32), is not reported in many case reports, case series studies, and prospective studies (7,33,34). A competing hypothesis has been proposed that NMS is a heterogeneous condition including catatonic variants and non-catatonic pathological reactions to antipsychotics (21,35,36). It may be argued that the diagnosis of catatonia, which is probably under-recognized, is likely to be missed in NMS unless it is particularly looked for, and catatonic symptoms may be over-shadowed or masked by NMS features. There are, however, no studies prospectively examining for catatonia throughout the longitudinal course of NMS to see if catatonic symptoms occur in all NMS at some stages in the progression of NMS.

This case series study of 14 prospectively identified episodes of NMS intends to examine:

1. the hypothesis that NMS is a catatonic variant and the catatonic syndrome can be diagnosed at some stages during the longitudinal course of NMS, and that in those catatonia is not diagnosed, possibly masked by NMS features, the NMS episodes do not differ from those with catatonia diagnosed in symptomatology (other than the absence of catatonia), clinical course, and treatment responses.
2. the competing hypothesis that NMS is a heterogeneous condition including catatonic variants and non-catatonic pathological reactions to antipsychotics, differing in symptomatology, clinical course, and treatment responses.
3. possible relationship between severe extrapyramidal side effects and NMS and the diagnostic significance of extrapyramidal features in NMS.

METHODS

Over an 8-year period, 14 episodes (13 patients) fulfilling the diagnostic criteria for NMS of Levenson (37) and Pope et al. (7) were prospectively identified at two psychiatric intensive care units, respectively. The less restrictive criteria were used to favor early detection and prompt intervention of NMS. All episodes met the criteria of DSM IV (11) and 7 of Caroff et al. (10) for NMS. The DSM IV criteria do not specify the minimum temperature for fever and those of Caroff et al. require a temperature above 38°C. The two sets of criteria are otherwise similar. Five cases were from the 23-bed Intensive Psychiatric Care unit (IPC) at the Tokanui Hospital, New Zealand from June 93 to October 95 and 9 from the 5-bed Acute Care Unit (ACU) at the Graylands Hospital, Western Australia from December 1995 to May 2001. The patients were under the care of the author and associated psychiatric residents.

Patients with NMS were examined at the time of NMS diagnosis and during the course of NMS by the author for catatonia using the diagnostic criteria of Rosebush et al. (38) and Lohr and Wisenewski (39). Patients at ACU were also assessed with the DSM IV criteria for catatonia (11, published in 1994) and the 23-item Bush-Francis Catatonia Rating Scale (BFCRS) (40, published in 1996). The 5 cases at IPC were retrospectively assessed using the latter two diagnostic instruments. Other studies on catatonia were concurrently conducted at the two units using the same sets of criteria for catatonia (21,41). Cases of acute catatonia identified were all treated with benzodiazepines and their progress closely monitored. Such concurrent catatonia studies helped identify 6 antecedent catatonic episodes, which progressed to NMS following exposure to antipsychotics. Moreover, suspected cases of evolving NMS with severe EPS were closely observed for possible NMS development. In all cases the presence and progression of catatonic symptoms, extrapyramidal effects, fever, autonomic disturbances, and delirium before and after antipsychotic exposure were noted. Relevant pre-admission information was gathered by reviewing medical charts of referring agencies.

The onset of NMS was taken when the diagnostic criteria were met and remission when all NMS symptoms were resolved or largely alleviated. Remission of NMS was hard to define in those when NMS developed in the context of catatonia. In such cases remission of both catatonic and NMS was taken. Antipsychotics and concurrent medications received at the time of the NMS diagnosis and for the week before the onset of NMS were noted. Extensive physical investigations were performed and consultations with the internist or neurologist obtained when necessary to exclude other possible causes.

All diagnosed episodes of NMS were managed as clinically indicated. Antipsychotic medications were ceased and supportive measures instituted. In all 14 episodes, benzodiazepines (lorazepam orally, diazepam intravenously or orally, or clonazepam intravenously or intramuscularly; parenteral lorazepam is not readily available in New Zealand and Australia) had been given for associated catatonia and/or for agitation. When

no prompt resolution of NMS/catatonic symptoms were attained, patients received other treatments including amantadine, bromocriptine or electroconvulsive therapy (ECT) or they be transferred to the medical units for intensive medical treatment. Resolution of fever, extrapyramidal effects, autonomic abnormality, delirium/impaired sensorium, and catatonic features were closely monitored. The final psychiatric diagnoses were made according to DSM IV (11) or DSM III-R (42) for those at IPC and revised retrospectively to DSM IV diagnoses.

Those NMS episodes with catatonia diagnosed (catatonic NMS) were compared with those in which catatonia was not diagnosed (non-catatonic NMS), noting their demographic characteristics, associated psychiatric diagnoses, catatonic subtypes, catatonic symptoms, antipsychotic and concomitant medications, and responses to benzodiazepines.

This was an observational study. Patients were not subjected to interventions or investigations beyond routine or usual clinical practice. The use of benzodiazepines for catatonia or agitation has been a widely accepted treatment. There were no ethical issues involved. Owing to their NMS, catatonic or delirious states, the patients were unable to give informed consent. Informed consent from the patients for the use of their clinical data for research purpose was obtained in retrospect after the NMS episodes.

RESULTS

Of the 14 episodes identified, 5 were from IPC (Patient 1–4) out of 1257 admissions (0.4%) over 28 months and 9 from ACU (Patient 5–13) out of 893 admissions (1%) over 66 months.

One patient (Patient 2) had 2 episodes. Eleven were male and 3 female (male/female: 1: 0.27) with a mean age of 30.6 years (18–49 years; SD = 8.57). Eleven were Europeans and 3 Polynesians. The peak temperature ranged from 37.5 to 41.2°C (mean = 38.1°C; SD = 6.94). Antipsychotics at the onset of NMS were: conventional antipsychotics 10, atypical antipsychotics 3 (Olanzapine 2, Risperidone 1), atypical and conventional combination 1. Of note, in all 3 of those on atypical antipsychotics NMS developed during the withdrawal from conventional antipsychotics (which were ceased because of severe extrapyramidal side-effects). Table 1 shows details of the 14 episodes of NMS.

Catatonia in NMS

At the time of the diagnosis of NMS, concurrent catatonia was diagnosed in 9 episodes (Patient 1 to 8). Eight fulfilled criteria for catatonia of Rosebush et al. (38), Lohr and Wisenewski (39), Bush et al. (40) and DSM IV (11); one (Patient 5) failed the criteria of Rosebush et al. and Lohr and Wisenewski but met the less restrictive criteria of Bush et al. and DSM IV. Five episodes (Patient 9 to 13) failed to meet all the criteria applied.

Antecedent Catatonia Progressing to NMS (NMS of Antipsychotic-converted Catatonia)

In 6 of the 9 episodes, catatonia was present before the commencement of antipsychotics. Five (Patient 1, 2 (episode a and b), 3, and 4) of these antecedent catatonia episodes were malignant

Table 1 Characteristics of 14 Episodes of NMS

Patient	Sex	Age	Temp (°C)	EP Effects	Diagnosis	Medications	Catatonia
1	M	41	38.2	CR, T, S	Schizoaffective Disorder	CPZ, HPL	Concurrent/ Antecedent
2a	M	38	40.2	LR, T, D, Tr	Psychosis NOS	HPL	Concurrent/ Antecedent
2b	M	38	38	CR, T, FG	Psychosis NOS	HPL	Concurrent/ Antecedent
3	M	30	38 C	CR, T	Schizophrenia	PMZ, HPL, CPZ (clozapine withdrawal)	Concurrent/ Antecedent
4	M	21	38.8	CR, S	Schizophrenia	ZPL	Concurrent/ Antecedent
5	F	23	37.5	CR, T, S, FG	Mania	HPL	Concurrent/ Antecedent
6	M	27	37.5	CR, T, D, Tr	Mania	CPZ, TFP, Li	Concurrent
7	M	34	37.7	CR, T, S	Schizophrenia	FPZ, PMZ, TDZ CZP, PRL	Concurrent
8	M	49	37.5	CR, T	Schizophrenia, Amnestic Disorder	HPL, TDZ	Concurrent
9	M	26	37.8	CR, T, S	Schizophrenia	TFP, HPL, Li	Nil
10	F	33	38	CR, T, S, FG	Mania	OZP, Li	Nil
11	F	20	37.8	RC, OP, FED, FG, S	Mania	OZP, HPL, TDZLi	Nil
12	M	18	38.3	CR, S, FG, PDT	Mania	RPD/ OZP, VAP	Nil
13	M	31	37.5	CR, FG, D	Schizophrenia	RPD	Nil

Temp = peak temperature; EP effects = extrapyramidal effects: CR = cogwheel rigidity, D = dysphagia, FED = flexor extensor limb dystonic posturing, FG = festinant gait, LR = leadpipe rigidity, OP = opisthotonus, PDT = perioral dystonic twitching, RC = retrocollis, T = tremor, Tr = trismus, S = sialorrhoea; Psychosis NOS = psychosis not otherwise specified; Medications: CPZ = chlorpromazine, CZP = carbamazepine, FPZ = fluphenazine decanoate, HPL = haloperidol, Li = lithium carbonate, OZP = olanzapine, PMZ = pimozone, PRL = propranolol, RPD = risperidone, TFP = trifluoperazine, VAP = sodium valproate, ZPL = zuclopenthixol decanoate.

with fever and autonomic abnormality and 1 (Patient 5) non-malignant [these were included in studies reported previously (21, 41)]. Following exposure to antipsychotics (from several hours to 2 weeks), in the 5 episodes of malignant catatonia the catatonic states worsened and marked extrapyramidal effects (severe parkinsonism with rigidity in all and dystonia in one [Patient 2, episode a]) emerged, fulfilling the diagnostic criteria for NMS; and in the non-malignant episode severe extrapyramidal effects developed with marked worsening of catatonia 5 days after antipsychotic treatment, followed 2 days later by fever and autonomic disturbances. Patient 2 had two other malignant catatonia episodes during the study period. Antipsychotics were not used for these two episodes and no NMS-conversion was observed.

Antipsychotic-induced Parkinsonian-catatonic Syndrome (NMS of Antipsychotic-induced Catatonia)

In 3 of the 9 episodes no preceding catatonia was noted (Patient 6, 7, 8). A catatonic-parkinsonian syndrome (with also dystonia in Patient 6) with fever and autonomic abnormality developed following treatment with antipsychotics (for 7 days in Patient 6, 7 and 1 day in Patient 8). These episodes may be regarded as the malignant form of neuroleptic-induced catatonia reported in the literature (16,19). In all 3, symptoms developed and progressed rapidly within 24 to 48 hours into a full blown syndrome. Table 2 shows the number of catatonic signs on the Bush-Francis Catatonia Screening Instrument (BFCSI) (40) and the catatonic subtype (retarded, excited, or mixed) in the antecedent and concurrent catatonic states. BFCSI includes the first 14 items on BFCRS. The 14 are either classical or the commonest catatonic signs more specific to the syndrome.

NMS with Catatonia vs. NMS without Catatonia

Preceding EPS and Delirium in NMS without Diagnosed Catatonia

In all 5 episodes of NMS with no diagnosed catatonia, it began with a severe extrapyramidal reaction—a parkinsonian syndrome in 3 (Patient 9, 10, 13) and parkinsonian-dystonic syndrome in 2 (Patient 11, 12)—with associated delirium. Investigations failed to reveal any concurrent medical causes for the delirium. The pre-NMS extrapyramidal syndromes showed poor responses to anticholinergics. Such a delirious-extrapyramidal syndrome lasted from 4 to 19 days (mean = 11.4 days, SD = 3.01) before progressing to a full-blown picture of NMS with appearance of fever and autonomic disturbances. Three patients (Patient 9, 10, 11) were on concurrent lithium therapy and one (Patient 12) on concurrent sodium valproate. In 3 episodes (Patient 10, 12, 13) the delirious-extrapyramidal reaction first developed with conventional neuroleptics. The conventional antipsychotics were hence stopped and atypical antipsychotics used (olanzapine for Patient 10, risperidone and then olanzapine for Patient 12, and risperidone Patient 13). The delirious-extrapyramidal syndrome, however, persisted and progressed (in 3 to 11 days) to NMS. In Patient 12, NMS first developed with risperidone. NMS symptoms improved with amantadine. On rechallenge with olanzapine, NMS symptoms recurred within hours.

Only 2 of the 9 catatonic NMS episodes (Patient 5 and 6) had preceding extrapyramidal (dystonic) reactions (not immediately preceding). Both responded to anticholinergic medications. There was no delirium associated with the preceding extrapyramidal reactions. None in the catatonic group was on

Table 2 Catatonia, Preceding Delirium and EPS, and Responses to Benzodiazepines in 14 NMS Episodes

Patient	Antecedent Catatonia	Concurrent Catatonia	Response to BZD	Other Treatments	Preceding Delirium	Preceding EPS	Duration of NMS/Catatonia* (Days)
1	7M	6R	Nil	ECT	Nil	Nil	14
2a	9E	8R	Transient	ECT	Nil	Nil	13
2b	9E	9R	Transient	ECT	Nil	Nil	10
3	8E	9R	Partial	Clozapine reinstatement	Yes	Nil	21
4	11R	11R	Nil	ECT	Nil	Nil	28
5	3U	4R	Prompt	—	Nil	Yes	2
6	—	7R	Prompt	—	Nil	Yes	4
7	—	8M	Partial	Amantadine	Nil	Nil	8
8	—	6R	Prompt	—	Nil	Nil	3
9	—	—	Nil	Supportive	Yes	Yes	14
10	—	—	Nil	Bromocriptine	Yes	Yes	4
11	—	—	Nil	Supportive	Yes	Yes	6
12	—	—	Nil	Amantadine, ECT	Yes	Yes	12
13	—	—	Nil	Supportive	Yes	Yes	6

BZD = benzodiazepines, EPS = extrapyramidal side effects, R = retarded catatonia, E = excited catatonia, M = mixed catatonia, U = undifferentiated. ECT = electroconvulsive therapy. *Duration of NMS/catatonia following diagnosis of NMS.

atypical neuroleptics. One patient (Patient 6) was on concurrent lithium and another (Patient 7) on concurrent carbamazepine therapy.

Responses to Benzodiazepines and Other Treatments

All 9 NMS episodes with catatonia received benzodiazepines along with cessation of antipsychotics following diagnosis of NMS for their catatonia/NMS. Three (Patient 5, 6, 8) showed marked improvement within a few hours with full resolution of both catatonic and NMS features within 2 to 3 days. Two (Patient 3 and 7) showed partial relief of symptoms. Two (Patient 2, episode a and b) showed transient symptom relief lasting only a few hours after intravenous diazepam. Two showed no significant responses (Patient 1 and 4).

NMS of Antipsychotic-converted Catatonia. The NMS episodes preceded by non-malignant catatonia (Patient 5) showed prompt responses to benzodiazepines (full remission within 2 days). The 5 episodes of antecedent malignant catatonia showed minimal responses to benzodiazepines and all 5 episodes evolved following exposure to antipsychotics into NMS. However, extra doses of benzodiazepines given after the NMS diagnosis produced partial or transient relief of NMS/catatonic symptoms in Patient 2 (episodes a and b) and Patient 3. None showed full responses to benzodiazepines and ECT was used in 4 of them with prompt resolution of catatonic and NMS symptoms.

NMS of Antipsychotic-induced Catatonia. In the 3 episodes with concurrent but no antecedent catatonia (antipsychotic-induced catatonia), all showed significant responses to benzodiazepines (2 prompt and full, Patient 6 and 8; and 1 partial, Patient 7, amantadine was subsequently added with prompt resolution of NMS symptoms).

Non-catatonic NMS. Benzodiazepines were used in the 5 NMS episodes without diagnosed catatonia. None showed significant responses after 3 days. Bromocriptine was subsequently used in Patient 10 and amantadine in Patient 12 with prompt resolution of NMS symptoms.

Extrapyramidal Effects

Various extrapyramidal features were prominent in all cases. In NMS of antipsychotic-converted catatonia, the emergence of prominent extrapyramidal effects marked the progression to NMS. Parkinsonian and dystonia were part of the antipsychotic-induced catatonia syndrome in those NMS of antipsychotic-induced catatonia. In all 5 episodes of non-catatonic NMS, it all began with a severe extrapyramidal syndrome with delirium progressing to NMS.

Laboratory Findings

The mean peak serum creatine phosphokinase (CPK) level was highest in the non-catatonic group (2652 U/L, 340–5680 U/L,

sd = 2120 vs. 2652 U/L, 170–4400 U/L, sd = 1488 in antipsychotic-converted catatonia and 397 U/L, 230–540 U/L, sd = 126 in antipsychotic-induced catatonia). While 7 in the catatonic group (in all 6 with antecedent catatonia) had low serum iron levels, only one in the non-catatonic group had low serum iron level (Patient 11; serum iron not done in Patient 10).

DISCUSSION

Catatonia, diagnosed with the use of a range of criteria, occurred in 9 (64%) of the 14 episodes of NMS concurrent with or antecedent to the NMS episodes. However, in 5 episodes, even with the least stringent criteria, catatonia was not diagnosed. The hypothesis that all NMS episodes are severe variants of catatonia and that NMS and catatonia are one single entity (20,27,29) cannot be substantiated on symptomatological grounds. Findings of this study provide some support for the competing hypothesis that NMS is a heterogeneous condition with catatonic variants and non-catatonic pathological reactions to antipsychotics (21,35,36).

Two forms of NMS with catatonia were discerned in this sample — the “NMS of antipsychotic-converted catatonia” and “NMS of antipsychotic-induced catatonia.” The “conversion” of antecedent malignant (lethal) catatonia following exposure to neuroleptics to NMS has been described by various authors (20–22). Five such cases were included in this sample. It has also been reported that antipsychotics may exacerbate non-malignant catatonia and transform it into NMS (43,44). One episode of this “malignant-shift” was observed in this study. The 3 episodes with catatonia and severe parkinsonism/dystonia developed following antipsychotic treatment may be regarded as the malignant form (with fever and autonomic abnormality) of neuroleptic (antipsychotic)-induced catatonia (16,19).

NMS episodes without catatonia pursued a different clinical course and appeared to represent a hyperthermic delirious extrapyramidal reaction to antipsychotics. All 5 episodes began with a severe extrapyramidal reaction with delirium and progressed to NMS. The pre-NMS extrapyramidal reactions with delirium showed no responses to anticholinergics. The findings provide some support for the hypothesis that extrapyramidal side effects and NMS are disorders on the same spectrum with NMS at one extreme of the spectrum. In the 5 non-catatonic NMS episodes, the delirious extrapyramidal reaction, often reported in the literature as an NMS-variant (45,46), appeared to be a transitional stage in the progression to NMS.

Extrapyramidal features were prominent in all 14 episodes. They were part of the antipsychotic-induced catatonia syndrome and their emergence marked the progression of NMS in those episodes of antipsychotic-converted catatonia. The significance of EPS in the diagnosis of NMS and the relationship between EPS and NMS merit more research attention.

The analysis of symptom progression helped discern the different forms of NMS in this study. There have been few

studies of the progression of symptoms in NMS. Several investigators have proposed that extrapyramidal symptoms often preceded other signs of NMS and that hyperthermia was a relatively late development (31,45,47,48). Velamoor et al. (49) analyzed the pattern of symptom development in clinical reports of NMS in the literature and found that in 62.7% of cases reviewed mental status changes (including clouding of consciousness and new-onset catatonia) and muscle rigidity arose before hyperthermia and autonomic dysfunction.

In the 5 episodes of NMS without catatonia, mental status changes (in form of delirium) and extrapyramidal symptoms/muscle rigidity preceded the development of hyperthermia and autonomic disturbances, consistent with the sequence proposed by Velamoor et al. (49). All 3 episodes of "NMS of antipsychotic-induced catatonia" pursued a fulminant course. A full blown syndrome developed within 1 or 2 days and it was difficult to distinguish the sequence of symptom progression. In the single case of non-malignant catatonia converted to NMS, symptoms also progressed following Velamoor et al.'s proposed sequence (mental status changes in form of confusion and worsening of catatonia). However, the 5 episodes of "NMS of antipsychotic-converted catatonia" with antecedent malignant catatonia pursued a different sequence. Hyperthermia and autonomic dysfunction arose before mental status changes (marked worsening of catatonia) and extrapyramidal symptoms/muscle rigidity. The temporal sequences of symptom progression observed in this study and their significance in differentiating the different forms or subtypes of NMS merit further studies.

NMS episodes with catatonia and NMS without catatonia differed not only in symptomatology and clinical course but also in treatment responses. While "non-catatonic" NMS episodes in the sample showed no significant responses to benzodiazepines, "catatonic" NMS episodes were more likely to respond favorably. Benzodiazepines are effective for acute catatonia (38,41,50) including antipsychotic-induced catatonia (16). The successful use of benzodiazepines in "mild variants" of NMS has been reported and prominent catatonic features were often described in these benzodiazepine-responsive NMS episodes (16–18). Francis et al. (27) in their retrospective review of 16 cases of NMS showed that benzodiazepines significantly relieved NMS symptoms, and concurrent catatonia occurred in 15 of the 16 NMS episodes (24).

However, benzodiazepines have not been uniformly effective in all cases of NMS. Addonizio et al. (47) in their review study showed that benzodiazepines were effective in 40% of the NMS episodes for which benzodiazepines were used. In some cases the effect was only transitory (51). Moreover, benzodiazepines did not prevent NMS from developing (31,52,53). In this case series study only the catatonic NMS episodes showed favorable responses to benzodiazepines. The NMS episodes of "antipsychotic-induced catatonia" without antecedent catatonia responded promptly to benzodiazepines. The responses to benzodiazepines of those NMS episodes of "antipsychotic-converted catatonia" varied, depending on

whether the antecedent catatonia was malignant or non-malignant. While the one episode with non-malignant antecedent catatonia responded promptly to benzodiazepines, those with malignant antecedent catatonia showed either no responses or only transitory or partial responses.

Findings of this study suggest that NMS may be subgrouped into catatonic and non-catatonic subtypes. The subtyping has potential clinical applications and pathophysiological implications. Catatonic and non-catatonic NMS are probably related in pathophysiology involving different pathways in the basal ganglia-thalamo-cortical circuits, which have been implicated in the mechanism of extrapyramidal syndromes, catatonia and NMS (54). Catatonia does not have a significant place in commonly used diagnostic criteria for NMS (7,10,11,37). It is subsumed under changes in mental status, along with clouding of consciousness and stupor in criteria for NMS of Caroff et al. (10) and Pope et al. (7). While the suggested renaming of NMS to "drug-induced hyperthermic catatonia" and the proposed criteria are not supported by the findings of this study, catatonia merits a better place in the diagnosis of NMS. In DSM IV catatonia is a specifier in mania and depression. The specifier provides the opportunity to define a more homogeneous subgrouping of individuals with the mood disorders. It is worth exploring the use of catatonia as a specifier in the diagnosis of NMS.

It is important to differentiate NMS from other movement disorder emergencies (55). Serotonin syndrome (SS), characterized by changes in autonomic, neuromotor, and cognitive-behavioural function, is a condition of serotonin hyperstimulation that can be a complication of treatment with serotonergic medications (56). There is an overlap in symptomatology between NMS and SS. The distinction between NMS and SS can be difficult in patients receiving both antipsychotic and serotonergic medications. SS is a differential diagnosis to consider in those episodes of NMS without catatonia in this study. One patient was on conventional antipsychotics and lithium carbonate (a serotonergic agent). The other 4 received atypical antipsychotics and 2 of them were on concurrent lithium therapy. Atypical antipsychotics have been implicated in SS (56,57,58). SS has been reported with combinations of atypical antipsychotics and various serotonergic agents including lithium (56,57,58). It has been suggested that the 5HT₂ antagonist effect of atypical antipsychotics may lead indirectly to overstimulation of 5HT_{1a} receptors and serotonin syndrome (56).

The clinical picture was in favour of NMS and not SS in the 5 episodes of NMS without catatonia. Symptoms evolved more gradually than is the case with SS (days rather than hours); all had severe muscular rigidity and extrapyramidal symptoms; and primary clinical features that differentiate SS from NMS including shivering, myoclonus, hyperreflexia and gastrointestinal symptoms were all absent (55,56). However, it is possible that concurrent serotonergic agents and serotonergic mechanisms play a role in the pathogenesis of this subtype of NMS without catatonia.

Owing to the small sample size, the bias toward milder forms of NMS detected early with prompt intervention, the

retrospective collection of data in some cases for features preceding admission, and the non-controlled nature of the benzodiazepine trial, the findings of this study need to be taken with caution. It is hoped that prospective studies with larger sample size are to be performed to evaluate the validity and clinical applications of the suggested subtypes of NMS.

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