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*Kandiah Sivakumar, MBBS, MRCPsych, DPM, *Consultant Psychiatrist, Maidstone Hospital Psychiatric Wing, Hermitage Lane, Maidstone, Kent ME16 9QQ*; Chike I. Okocha, MBBS, *Registrar, Maidstone Hospital Psychiatric Wing, Maidstone, Kent*

*Correspondence

Risk for Definite Neuroleptic Malignant Syndrome

A Prospective Study in 223 Consecutive In-patients

HAGGAI HERMESH, DOV AIZENBERG, ABRAHAM WEIZMAN, MARGO LAPIDOT, CATHERINA MAYOR and HANAN MUNITZ

The occurrence of neuroleptic malignant syndrome (NMS) was studied prospectively in two series of consecutive psychiatric in-patients ($n = 223$). The first group ($n = 120$) suffered from schizophrenia and was treated only with haloperidol. The second group ($n = 103$) was treated with diverse neuroleptics. All patients were on a single antipsychotic agent with no anticholinergic drug as prophylaxis. The incidence of full NMS per admission and first neuroleptic exposure was 5/223 (2.2%). Patients with bipolar affective disorder and those treated with injections were significantly over-represented in the NMS group.

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Neuroleptic malignant syndrome (NMS) has recently been attracting increasing attention, as shown by the rising number of publications annually on this issue (Kellam, 1987; Shalev *et al*, 1989). This interest is due to the alarming mortality rate which, in the past, was higher than 20% of NMS episodes (Shalev *et al*, 1989; Lazarus *et al*, 1989), and the awareness that this risky side-effect is not as rare as had been previously thought (Addonizio *et al*, 1986; Pope *et al*, 1986). However, even basic data about NMS are still scarce, including prevalence and incidence as well as figures concerning mortality rate and the risk per exposure to a neuroleptic. According to some studies, NMS is a very rare adverse side-effect occurring in 0.02–0.07% of neuroleptic-treated patients (e.g. Spiess-Kiefer *et al*, 1988). Based on his two-year survey of all cases of stupor in central South Wales, Kellam (1987) estimated "the annual incidence of NMS as one case per 1–5 million population, an incidence that would give an average psychiatrist about an even chance of seeing one case during his working lifetime". Most others reported an incidence of from 0.12% (e.g. Deng *et al*, 1990) to 0.4%. However, some studies (Addonizio *et al*, 1986; Pope *et al*, 1986; Keck *et al*, 1987) found an incidence closer to 1–2%, as did Delay *et al* (1960) in their early descriptions of NMS.

In order to estimate the incidence of NMS we conducted a prospective study, using standardised diagnostic criteria of NMS in newly admitted patients undergoing their first neuroleptic treatment.

Method

Criteria for full-blown NMS were those suggested by Levenson (1985), Lazarus *et al* (1989) and Pope *et al* (1986).

(a) Hyperthermia (axilla > 37.8 °C, per oral > 37.9 °C, per rectum > 38 °C). It is considered by all reviews and epidemiological studies as a critical sign. In the absence of elevated temperature the diagnosis of NMS would be inconclusive and would not be included in this study.

(b) Additional autonomic disturbances. At least two of the following: increased diastolic blood pressure above baseline of more than 20 mmHg, tachycardia of more than 30 beats/min above baseline pulse, prominent diaphoresis, incontinence, and tachypnoea.

(c) At least two of the following marked motor and extrapyramidal signs: hypertonus of either cogwheel or lead-pipe type, pronounced tremor, choreiform and dyskinetic movements, festinating gait and flexor–extensor posturing, prolonged retrocollis, opisthotonus, trismus, and considerable sialorrhoea.

(d) Clouded mentation (i.e. marked sedation, delirium, stupor, or coma).

(e) Clearly elevated levels of serum creatine phosphokinase (CPK) (>500 IU/ml, normal upper level 200 IU/ml) and white blood count (WBC) (>14 000/mm^3).

All NMS patients were also examined by an internist within three days of the episode to rule out any other diagnosis. Hyperthermia and at least three out of the other four criteria had to be met for a definite diagnosis of NMS.

The study was conducted simultaneously on the two acute psychiatric wards of Geha Psychiatric Hospital. All participants had been in-patients for at least a week while on neuroleptics.

Two groups of neuroleptic-treated patients comprised the study. Group 1 was made up of patients with schizophrenic disorder according to DSM-III criteria ($n=120$) (American Psychiatric Association, 1980). They were treated with haloperidol, either 10 mg/day ($n=60$) or 20 mg/day ($n=60$), in fixed doses for at least two weeks (mean equivalent chlorpromazine 750 mg/day). They were randomly allocated to one of the two doses as prospectively designed for another haloperidol study. Group 2 comprised 103 consecutive patients, none of whom had participated in Group 1. The study of this second group began immediately after the completion of the study of Group 1. The patients included in this group had either schizophrenic ($n=72$) or bipolar affective ($n=31$) disorder. Patients in the second group were treated with diverse neuroleptics, mostly perphenazine 37%, haloperidol 33% and levomepromazine 27% (mean (s.d.) equivalent chlorpromazine 657 (122) mg/day). In both groups each patient was treated with a single neuroleptic preparation throughout his/her participation in the study. Anticholinergics were not used as a prophylaxis before significant extrapyramidal side-effects appeared, and no benzodiazepines were used except briefly for some acute dystonias. Lithium carbonate treatment was not started during the study. However, at admission, 24 patients were maintained on lithium, and lithium administration was continued in 19 of them. The occurrence of NMS was studied at admission and monitored during the first course of neuroleptic treatment. Patients with known past NMS ($n=2$) were not included.

Patients from the haloperidol group were examined for NMS only if there had been clinical clues to the syndrome, while every patient from the second group was systematically and extensively investigated throughout the first three weeks. Follow-up in the second group included thrice daily measures of body temperature, pulse, blood pressure, excessive sweating, altered level of consciousness, and extrapyramidal signs. Muscle enzymes and WBC were taken two to three times per week. Following the extensive search for NMS, subsequent follow-up was based on the presence of signs suggesting NMS. The duration of follow-ups of Group 1 and Group 2 was 4.2 (s.d. 1.2) weeks (range 1.0–6.3 weeks) and 3.4 (s.d. 1.1) weeks (range 1.0–6.6), respectively.

Results

The 95% confidence interval for incidence in our acute wards of definite NMS per admission and first neuroleptic exposure was 2.2%–0.9%.

Two patients from the haloperidol group had NMS (1.7%), as had three from the other group (2.9%) (Table 1). Two patients, one from each group, were admitted with the syndrome. One of these latter had a recurrent NMS during re-exposure to another low-potency neuroleptic.

All patients reached maximal levels of CPK that were 2.6–17.0 times higher than their pre-NMS and post-NMS levels. In all cases in which NMS was definitively diagnosed, CPK levels were at least 1.6 times higher than the enzyme non-NMS levels, as documented in previous hospital admissions or the post-NMS period. In all patients, CPK levels reduced to normal range after the NMS event. At admission, mean CPK level of 103 non-NMS patients from Group 2 was 671 (s.d. 269) IU/l. It dropped in most patients (85%) to reach a mean level of 392 (s.d. 166) IU/l at the end of one week on neuroleptic. This decrease contrasted with the rise of CPK observed in the three NMS patients who developed the complication on first exposure to neuroleptic in the ward (from 298, 413, and 983 IU/l to 1254, 1017, and 3678 IU/l respectively, from 564 (s.d. 299) IU/l up to 1983 (s.d. 1202) IU/l). Maximal CPK levels for the two

Table 1
Characteristics of neuroleptic malignant syndrome (NMS) and non-NMS patients during first course of neuroleptic therapy in two neuroleptic groups

	Diagnosis		Neuroleptic			Sex M:F	Psychiatric diagnosis		Route of administration
			No.	Agent	mg/day				
Group 1	NMS	$n=2$	2	HPL[1]	10	2:0	2 schizophrenia	2*	intramuscular
Haloperidol only	No NMS	$n=118$	58	HPL	10	68:50	118 schizophrenia	35	intramuscular
			60	HPL	20			83	oral
Group 2	NMS	$n=3$	2	LPZ[2]	250, 500	2:1	0 schizophrenia	2*	intramuscular
			1	PPZ[3]	32		3* bipolar	1	oral
Neuroleptics	No NMS	$n=100$	37	PPZ	24–40	56:44	72 schizophrenia	40	intramuscular
			34	HPL	10–15		28 bipolar	60	oral
			26	LPZ	250–400				
			3	others					

1. HPL = haloperidol.
2. LPZ = levomepromazine.
3. PPZ = perphenazine.
*$P<0.06$.

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other patients who were admitted with NMS were clearly elevated compared with levels at admission and discharge periods (62–176 and 50–981 IU/l v. 1211 and 1667 IU/l respectively).

A comparison was made for alterations in CPK levels during the first week between patients who were treated orally ($n = 42$) and patients treated with injections ($n = 61$). No significant difference in CPK changes (delta CPK) was observed in group 2, between non-injected and injected patients (Student's t-test, non-paired, two-tailed, $t = 1.35$, NS).

Fever persisted for at least 12 hours. It was measured as elevated on no less than three occasions and its maximal values ranged from 38.3 °C orally to 40.5 °C, per rectum. Four patients were excluded following consultation with the internist who attributed the constellation of signs to alternative diagnoses (systemic infection in two cases, marked dehydration in one case, and multiple injuries in one case). The incidence of partial forms of NMS (i.e. possibly aborted forms, that fulfilled only some criteria of NMS) is currently under evaluation.

In the NMS group, patients who had bipolar affective disorder (3/5) and those treated with injections (4/5) were significantly over-represented ($P < 0.06$, Fisher exact tests, 2×2). All three bipolar NMS cases belonged to the second group despite the fact that this psychiatric diagnosis accounted for only a quarter of the group's population. Age and sex distribution of the patients who developed NMS, and the neuroleptics that were involved in inducing it, were not significantly different in the two groups. Lithium carbonate was associated with one case of NMS, which had been diagnosed at admission. NMS was either detected at admission ($n = 2$) or during first neuroleptic course ($n = 3$).

The syndrome was diagnosed within the first eight days from commencement of neuroleptic course. In the two NMS cases that emerged before admission, the complication appeared within two to six days of initiation or considerable change in neuroleptic treatment regimen.

Discussion

In a prospective survey of 223 neuroleptic-treated patients, five developed NMS during the study period. The criteria we required were somewhat stricter than in most other research concerning the epidemiology of NMS as the cases had to fulfil each of the commonly used criteria (Levenson, 1985; Pope *et al*, 1986; Lazarus *et al*, 1989). In three cases out of the five, the syndrome appeared following the first neuroleptic administration and it yielded a risk of about 1.3% per neuroleptic exposure. These figures approximate to those of several other studies (Pope *et al*, 1986; Keck *et al*, 1987), and especially those of Addonizio *et al* (1986) who reported an incidence of 2.4% of definite NMS in their 82 consecutive male patients. However, much lower rates have been published in recent prospective studies (e.g. Spiess-Kiefer *et al*, 1989; Deng *et al*, 1990), which reported an incidence lower by one or two orders of magnitude. Thus, there appears a divergence in incidence ranges of over a hundred-fold between various investigators.

It should be kept in mind, however, that conclusive identification of the risk factors is problematic in this study as well as in others. A second-order univariate relationship can confound the apparent associations between NMS and other variables (e.g. affective cases are frequently treated with lithium), and young male patients are possibly more agitated and therefore treated with injections and high doses more often than older females (Keck *et al*, 1989). A larger number of NMS cases is needed in order to obtain enough statistical power to ascribe these risk factors to NMS.

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*Haggai Hermesh, MD; Dov Aizenberg, MD; Abraham Weizman, MD; Margo Lapidot, PhD; Catherina Mayor, MD; Hanan Munitz, MB BS, *Geha Psychiatric Hospital, Beilinson Medical Center, Petah Tikva and Sackler School of Medicine, Tel Aviv University, Israel*

*Correspondence: *Geha Psychiatric Hospital, PO Box 102, Petah Tikva 49 100, Israel*

Neuroleptic Malignant Syndrome Presenting as Hyperosmolar Non-ketotic Diabetic Coma

M. BALZAN and J. M. CACCIOTTOLO

A 50-year-old man presented with hyperosmolar non-ketotic diabetic coma associated with the neuroleptic malignant syndrome (NMS) after intramuscular treatment with haloperidol. It is suggested that NMS may occur as a complication of uncontrolled diabetes mellitus with dehydration. Conversely, NMS might precipitate diabetic coma in patients with previously well controlled blood glucose.

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Case report

A 50-year-old white man in diabetic coma was transferred to a general medical hospital from a psychiatric unit. Over the previous 15 years he had suffered from recurrent episodes of depression with psychotic features. He did not have any other medical problems and was unaware of his glucose intolerance. Ten days earlier he had been admitted to the psychiatric hospital with retarded depression and was treated with tricyclic antidepressants and trifluoperazine, 1 mg twice daily. This treatment had been given on three other separate occasions with consequent improvement.

Over three days, the patient developed catatonia and was treated with haloperidol 5 mg intramuscularly every six hours. Electroconvulsive therapy was performed on two occasions with only slight improvement. The attending anaesthetist recorded wide fluctuations in blood pressure with readings varying from 160/100 to 190/130 mmHg (mean 170/110 mmHg). Two days before his transfer, moderate muscle rigidity and a fine Parkinsonian tremor were noted. There were no dyskinetic movements. In view of his deteriorating general condition, increasing rigidity, and progressive unresponsiveness, he was referred to a general medical hospital for intensive supportive care.

In the emergency room he was comatose. His respiratory rate was 24 per minute, regular both in frequency and in amplitude. He was grossly dehydrated, had a small volume pulse of 120 beats/min, a blood pressure of 100/60 mmHg and a rectal temperature of 40 °C. Blood tests showed: glucose 45 mmol/l, haemoglobin 16 g/dl, white cell count 23 000/mm^3, urea 23.8 mmol/l, creatinine 200 μmol/l, Na^+ 145 mmol/l, K^+ 4.5 mmol/l, pH 7.34, HCO^{3-} 20.2 mmol/l, pO_2 120 mmHg, creatinine phosphokinase (CPK) 840 U/l (normal 0–100 U/l), plasma osmolality 368 mosm/kg. The chest X-ray and the electrocardiogram were unremarkable. Urine analysis showed heavy glucosuria, no ketonuria or indeed any other abnormality.

Three litres of fluid were rapidly infused. Central venous pressure measured in the intensive care unit was 2 cm water and a further three litres of fluid were infused. An insulin infusion was started at eight units per hour. Treatment with ice-packs and rectal paracetamol had little effect on his body temperature. He was also treated with intravenous cefuroxime and low-dose subcutaneous heparin.

Twelve hours after admission, his fluid deficit and high blood glucose had been corrected. His general condition improved, but consciousness remained clouded. There was extreme muscle rigidity, tremors of all four limbs, and at times opisthotonus and trismus. Computerised tomography of the brain did not show any cerebral oedema or any other abnormality. Blood and urine cultures taken before and after the start of antibiotic therapy were repeatedly negative.

He was treated with intravenous dantrolene 60 mg every six hours. There was a slight decrease in muscle rigidity, but overall there was no clear improvement. Twenty-four hours after admission he became extremely tachypnoeic (50–60 min). Arterial blood gases on 50% oxygen showed a pO_2 of 73 mmHg and pCO_2 of 32.9 mmHg. An intravenous infusion of heparin at a dose of 1500 U/h was started.

Up to day nine, his general condition remained unchanged, with temperature persistently above 38.5 °C (Fig. 1), continuous unstable tachypnoea of around 40/min, and unabating muscle rigidity. His CPK was persistently