Neuroleptic malignant syndrome in Malaysia: A University Hospital experience

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Summary

The neuroleptic malignant syndrome (NMS) is a potentially fatal complication of antipsychotic therapy. A retrospective study of nine patients seen over six years at the University Hospital, Kuala Lumpur (UHKL), is described. The estimated annualised incidence was 1.2 per 1000 in-patients with psychosis. No ethnic difference was detected. Clinical features were similar to experiences elsewhere, with wide variability seen in the severity of illness. The neuroleptic drugs implicated were haloperidol, trifluoperazine, chlorpromazine, fluphenazine and clopenthixol. Treatment consisted of withdrawal of offending drugs and supportive measures. Specific therapy was given to five patients. There was one death. At follow-up no deterioration was detected. A different neuroleptic drug was successfully re-introduced in four patients. In view of the wide usage of major tranquillizers, a high degree of clinical awareness of this serious complication is necessary for early diagnosis to reduce morbidity and mortality.

Key-words: Neuroleptic malignant syndrome, Malaysia, antipsychotic drugs, outcome.

Introduction

The neuroleptic malignant syndrome (NMS) is now a well-recognised complication of antipsychotic drugs. It is characterised by hyperpyrexia, muscle rigidity, elevated creatine kinase (CK) and altered sensorium which develop soon after commencement of neuroleptic therapy. This rare, yet potentially fatal idiosyncratic response has been reported following a variety of major tranquillizers and also withdrawal from anti-Parkinsonian therapy. Since the original description by Delay and Deniker (1960),[1] a different picture of NMS has emerged. Instead of a uniformly "malignant" clinical course, wide variability in severity and outcome has been observed. Fatality rates have fallen, possibly reflecting an increased awareness of the syndrome, better management, and changes in selection of cases for reporting. Nonetheless, despite extensive documentation in t he literature, diagnosis of NMS is often missed or delayed.

The largest series to date from medical college hospitals[2] includes nine patients. Single cases[3,4] and a study of four patients[5] have been reported from Malaysia. We describe here our experience with nine patients treated at the University Hospital, Kuala Lumpur (UHKL) between May 1983 and April 1989. Two interesting forms of presentation are described.

Case Reports

Patient M.C.

A 65-year-old Chinese woman was admitted on 5.12.88 for change in behaviour and tremor. The patients's intellectual function had been declining for two years. For the previous six months, she had become more withdrawn, forgetful and occasionally agitated. She would pace aimlessly about the house, even at night. Tremor of the hands had been noted for the past five years. In the last month, she became increasingly restless, with poor concentration and bizarre behaviour. On 12.11.88, oral haloperidol was prescribed. She deteriorated further, becoming confused and rigid, with worsening of tremor. No intramuscular injection was given.

On admission to UHKL, she had low grade fever, with blood pressure of 120/80 mmHg and pulse rate of 78/minute. She was withdrawn, with reduced facial expression. On mental status testing, she was confused, disoriented and responses were limited. Tone was increased, with cogwheel rigidity and pill-rolling tremor. Tendon reflexes were brisk and the jaw jerk was exaggerated. Glabellar reflex was present. The clinical problems were identified as Parkinsonism and dementia.

Routine blood investigations were normal. Electroencephalography showed abnormal background activity with focal delta activity over the left temporal region. CSF examination and contrast CT brain scan were normal. Extensive search for evidence of infection was negative. The serum CK was markedly elevated, with peak at 3075 IU/L. A final diagnosis of Alzheimer's disease with super-imposed NMS was made. Bromocriptine 2.5 mg b.d. was started. There was gradual improvement in confusion and extrapyramidal symptoms, with total duration of illness of six weeks.

Patient A.C.B.

In Novemebr 1984, an 18-year-old Chinese schoolgirl developed episodes of abnormal behaviour. She had viral encephalitis in December 1983, with eventual recovery of cognitive functions. Focal seizures were treated with carbamazepine. This was discontinued in mid-November 1984 on cessation of seizures. Three days later, there were episodes of bizarre behaviour, consisting of shouting and running aimlessly. Carbamazepine was restarted but concentration remained impaired and repetitive purpose-less acts were witnessed. She gradually became confused, negativistic, mute and frightened. She was mostly withdrawn, and occasionally aggressive. There was soliloquy, echolalia and perseveration of speech.

She was admitted to a regional hospital, where catatonic stupor was diagnosed. Brain CT was normal. There was no response to trifluoperazine nor haloperidol given subsequently. Eight sessions of electroconvulsive therapy were then given between 26.12.84 and 11.1.85. In late December, she became stiff, with abnormal posturing and tongue protrusion. Later, she developed tonic spasms of the limbs, for which clonazepam and baclofen were added. On 12.1.85, she became febrile with cough, and antibiotics were started. Chest radiography then was normal.

On admission to UHKL on 17.1.85, she was febrile, sweating and mute, with a blank stare. There was tachycardia and blood pressure was labile, with elevation up to 160/90 mmHg. Reflexes were symmetrical. There was hand tremor and ankle clonus, and intermittent tongue protrusion. Repeated generalised seizures were seen. In addition, she had diffuse rigidity which was persistent regardless of clinical seizure activity. The cerebrospinal fluid pressure was 21 cm of water and the protein borderline high at 0.55 g/L; it was otherwise normal. Electroencephalography (EEG) showed bilateral paroxysmal slow wave activity; subsequently focal abnormality was seen variously over the left posterior quadrant or left parietal and temporal areas, with sporadic sharp transients. Status partial

epilepsy was diagnosed. Intensive anticonvulsant therapy was administered, including intravenous diazepam, thiopentone, carbamazepine, phenytoin and sodium valproate. In addition, antibiotics were given for urinary tract infection.

Despite substantial improvement of EEG abnormalities, she continued to be febrile, mute and rigid with elbows and fingers flexed, and dystonic posturing of the right foot. Other foci of infection had been excluded. Thus, on 25.1.85, diagnosis of concomitant NMS was considered. Serum CK was found to be elevated, peaking at 678 IU/L.

Neuroleptic drugs had already been discontinued at entry. On 28.1.85 bromocriptine was given in gradually increasing doses up to 5 mg q.i.d. Features of NMS abated gradually over four weeks. There was stabilization of complex partial epilepsy but she had residual intellectual impairment which improved slowly. At the latest review in November 1991 she was doing secretarial work.

Nine patients developed NMS after taking anti-psychotic drugs. Seven had functional psychosis while two had status epilepsy and Alzheimer's disease respectively. All fulfilled diagnostic criteria for NMS as proposed by Levenson[6] i.e. presence of (i) three major or (ii) two major and four minor manifestations. The diagnosis of NMS was often not considered at the outset. With increasing experience, it was suspected earlier; in three cases, as soon as symptoms developed. The admission diagnoses, demographic data and clinical course are shown in Table I. Age range of the patients was 18 to 65 years. Four patients were male and five female. None had history of alcohol abuse, or family history of malignant hyperthermia.

The cardinal clinical features are listed in Table II. Less commonly occurring clinical features and laboratory abnormalities are summarised in Tables III and IV. Myoglobinuria was not detected in any of the patients, including K.N. who had acute renal failure[4] All patients had EEG. Except for A.L., all were abnormal, showing mainly diffuse slow wave activity (seven) or focal slowing (one – M.C.). CSF was examined in all except C.M. CSF protein was mildly raised in W.Y.Y. and borderline in three patients (A.C.B., N.H. and A.I.). In three patients (A.C.B., A.I. and N.H.) brain CT was normal. In the fourth (A.L.), the left lateral ventricle was dilated. Complications of NMS were seen in two patients: renal failure in K.N.; and respiratory failure in A.I. and K.N. who both required mechanical ventilation. The latter also had aspiration pneumonia.

Neuroleptic drugs were stopped as soon as diagnosis of NMS was considered. Rehydration and antipyretic measures were immediately started. Three patients recovered with supportive measures. One patient absconded after four weeks of improvement. Specific drugs were given orally to five patients who were very ill. Response was seen following bromocriptine (A.C.B. and M.C.) and combination of diazepam and bromocriptine (K.N. and C.H.K.). A.I., the earliest recorded case, was the sole patient who died despite treatment with diazepam and dantrolene sodium. The remaining patients improved over periods ranging from 12 days to nine weeks. A.C.B., who had status epilepsy, suffered residual intellectual impairment. No deterioration was seen in the survivors during follow-up ranging from 2 to 83 months.

Discussion

NMS appears to be a worldwide phenomenon. In addition to extensive documentation from Europe, the Americas and Australasia, there have been reports from Japan,[7] China,[8] India,[9] Israel,[10] and Africa.[11,12]

The incidence of NMS ranges from 4 to 14 per 1000 treated persons (quoted in Kellam[13]). In a recent survey the annual frequency in a short-term psychiatric hospital was as low as 0.7 per 1000 treated

Table I
Summary of presenting features and clinical course of NMS in 9 patients

Patient	Age (yrs)	Sex	Race*	Primary Diagnosis	Admission Diagnosis	Neuroleptic Drug	Route of Administration	Time Taken for diagnosis	Duration of illness	Outcome	Neuroleptic Re-introduced	Follow-up (months)
A.I.	21	M	M	Schizophrenia	Viral encephalitis	Chlorpromazine	i.m.	3 days	12 days	Death	–	0
A.C.B.	18	F	C	Status epilepsy	Catatonic stupor	Trifluoperazine Haloperidol	oral oral	4 weeks (8 days after admission)	4 weeks	Impaired intellect	–	83
N.H.	20	F	M	Schizophreniform disorder	Catatonic schizophrenia	Chlorpromazine Fluphenzine#	oral i.m.	8 days (3 days after admission)	2 weeks	Recovered	Haloperidol	32
C.M.	44	F	C	Major depression	Catatonic depression	Chlorpromazine Haloperidol#	oral i.v.	2 days	2 weeks	Recovered	Thioridazine	16
K.N.**	41	F	M	Schizophrenia	NMS	Haloperidol	oral	At onset	9 weeks	Recovered	Thioridazine	46
W.Y.Y.	19	M	C	Schizophreniform disorder	NMS	Chlorpromazine	oral	At onset	4 weeks	Absconded	–	0
C.H.K.	26	M	C	Bipolar affective disorder	Drug-induced extrapyramidal syndrome	Fluphenazine Haloperidol Chlorpromazine Clopenthixol#	i.m. oral oral, i.m. oral	2 days	3 weeks	Recovered	Thioridazine	27
M.C.	65	F	C	Alzheimer's disease	Parkinsonism	Haloperidol	oral	2 days	6 weeks	Recovered	–	16
A.L.	40	M	E	Bipolar affective disorder	NMS	Haloperidol# Chlorpromazine Thioridazine	oral, i.v. oral oral	At onset	12 days	Recovered	–	2

Legend

* *M – Malay*
C – Chinese
E – English

\# *most likely cause of NMS*

** *previously reported (Reference 4)*

Table II
Clinical features of NMS in 9 patients

	A.I.	A.C.B.	N.H.	C.M.	K.N.	W.Y.Y.	C.H.K.	M.C.	A.L.
MAJOR MANIFESTATIONS*									
Peak temperature (°C)	40 PA	39.3 PA	40.5	38	40.5	39	37.8 PA	39 PA	39.5
Rigidity	+	+	+	+	+	+	+	+	–
Peak CK (IU/L)	>3000	678	2070	1500	19520	1950	1792	3075	787
MINOR MANIFESTATIONS*									
Peak heart rate (beats per minute)	140	124	140	120	150	120	112	120	130
Peak (trough) blood pressure (mmHg)	190/140	160/90	(90/70)	140/90	110/50	155/110	140/80	160/90	(90/70)
Tachypnoea	+	+	+	+	+	+	–	+	+
Diaphoresis	–	+	–	+	+	+	+	–	+
Altered sensorium	+	+	+	+	+	+	+	+	+
Peak white cell count x 10^9/L	15.1	10.7	8.5	12.5	19.2	10.3	12.3	8.7	16.3

Legend
* *Criteria for guidance in the diagnosis of NMS (after Levenson, 1985)*
PA *Per axilla*

patients.[14] The University Hospital, Kuala Lumpur is a tertiary referral centre with a medical department and short-stay psychiatric department. Our annualised incidence was 1.2 per 1000 in-patients with psychosis. It is comparable with that of China where the incidence was reported to be 1.23 cases per 1000 in-patients at a large psychiatric hospital.[8] Comparison with other series is difficult because of the use of different denominators.

Table III
Less common clinical features of NMS in 9 patients

	A.I.	A.C.B.	N.H.	C.M.	K.N.	W.Y.Y.	C.H.K.	M.C.	A.L.
Mutism	+	+	+	+	+	+	+	+	–
Tendon reflexes	↑	N	N	N	↑	↑	N	N	N
Gaze abnormality	+	–	–	+	–	–	–	–	–
Seizure	+	+	–	–	–	–	–	–	–
Salivation	–	–	–	+	–	–	–	–	+
Dysphagia	–	–	–	–	+	–	–	–	–
Respiratory failure	+	–	–	–	+	–	–	–	–

Legend: *N = Normal, ↑= Increased, + = present, – = absent*

Table IV
Laboratory investigations in 9 patients with NMS

	A.I.	A.C.B.	N.H.	C.M.	K.N.	W.Y.Y.	C.H.K.	M.C.	A.L.
Peak (trough) potassium (mmol/L)	5.6	(2.8)	N	(3.4)	N	(3.2)	(3.2)	(3.2)	(3.1)
Peak (trough) serum sodium (mmol/L)	150 (116)	N	N	N	154	N	N	N	N
Peak blood urea (mmol/L)	18.9	4.4	10.2	8.7	39.7	5.8	4.8	7.6	5.2
Plasma creatinine (umol/L)	128	63	–	84	821	117	97	75	123
Serum calcium (mmol/L)	–	1.35	–	2.3	2.72	2.22	–	2.2	2.0

NMS has been reported to be triggered by external heat load,[10,15] but the incidence was not appreciably higher in Malaysia where the usual temperature range is 21° to 32° Celcius.

The averaged racial distribution of in-patients with psychosis at UHKL was Malay 17.6%, Chinese 52.6%, Indian 28.3% (mainly South Indians) and others 1.4%. There were equal numbers of Malay and Chinese patients in our series (Table I). Although the figures are small, racial predilection for NMS does not appear to be evident in Malaysia. There was no Indian with NMS although it has been previously documented in South Indians.[9]

Risk factors for NMS were dehydration, exhaustion, and high doses of neuroleptics as previously described.[15,16] The oral route was as frequently implicated as parenteral injection in our patients, unlike in other series where the latter was a risk factor. Haloperidol was most frequently implicated in our series (six of nine patients). However, this is likely to reflect its wide usage, particularly for severe psychosis. Thus, in common with other studies, none of the antipsychotic drugs was shown to have a higher propensity for inducing NMS. Depot formulations may be expected to cause more prolonged illness, but this was not seen in the only case clearly related to fluphenazine (N.H.). Antidepressants, and withdrawal of neuroleptics or antiparkinsonian drugs were not implicated in our series.

Recent reviews have highlighted variable clinical severity of NMS[13,17] in contrast with the fulminant course described earlier. While the number of reported cases has been increasing, mortality rates have fallen, from 25% to 11.6% before and since 1984.[18] Our mortality rate was 11.1%. Spontaneous recovery without specific drug therapy is increasingly described and the Asian experience appears to be similar.[8] Our patient numbers were insufficient for analysis of poor prognostic factors. Of these, organic brain syndrome was present in only two patients, and the sole patient with renal failure recovered. Long-term outcome[19] was good once the acute illness had subsided. Protracted[20] or recurrent[21] NMS was not seen.

The question of whether "Neuroleptic malignant syndrome" represents a distinct clinical entity, or rather a group of disparate conditions, has been raised.[22,2] To emphasise their heterogeneity, use of the noncommittal label *"extrapyramidal symptoms with hyperpyrexia"* has been advocated. In our patients, a unitary syndrome with a consistent constellation of clinical and laboratory features was identifiable. No cause other than neuroleptic therapy could be implicated as the basis for hyperpyrexia, rigidity, elevated CK levels, leukocytosis and cerebral dysfunction. Infective complications outside the central nervous system developed in some patients only after appearance of extrapyramidal signs and stupor. Those patients with functional psychoses, in whom lethal catatonia might be considered, in fact deteriorated after commencement of neuroleptic drugs.

While recognising NMS as an entity, strict diagnostic criteria should be used to avoid overdiagnosis, because NMS has no unique diagnostic features, and there is overlap with the neuroleptic-induced extrapyramidal syndrome.

Since NMS is potentially fatal, constant vigilance should be maintained for patients on neuroleptic drugs, particularly in the early weeks after initiation. Phenothiazines and other major tranquillizers should be used after careful consideration of the indications.

NMS has been attributed to a number of mechanisms, probably peripheral, the most frequently suggested being dopaminergic blockade. Specific therapy includes dantrolene, bromocriptine, subcutaneous lisuride, L-dopa and amantadine; and augmentation of their effects with benzodiazepines and anticholinergic agents. Combination of drugs may be required for treatment of severe disease.

The controversial use of electro-convulsive therapy (ECT) has its proponents.[23] A.C.B. received ECT for symptoms attributed to catatonic stupor without improvement in NMS, while status epilepsy was perpetuated. In W.Y.Y., ECT was subsequently safely given to treat acute schizophreniform disorder. Thus, ECT does not seem to be useful for NMS; neither does NMS appear to be aggravated.

For those patients who recover from NMS, cautious re-introduction of a different neuroleptic drug may be considered[24] if further antipsychotic therapy is indicated. Four patients had gradually increasing doses of a different oral neuroleptic thioridazine (three) and haloperidol (one) without further incident.

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