A REVIEW OF NEUROLEPTIC MALIGNANT SYNDROME: INCIDENCE AND FEATURES IN MALTA

A. Grech, J.R. Saliba

ABSTRACT:

This paper describes Malta's first sample of Neuroleptic Malignant Syndrome (NMS) and reviews the current literature. A retrospective sample of all diagnosed cases of NMS was reviewed using Pope's (1986) criteria. Twelve cases were identified yielding an incidence of 0.67%. The range of associated risk factors and complications agreed with other reports. There were also two cases of uncontrolled diabetes. Treatments commonly used were Bromocriptine and Levodopa. There were no deaths due to NMS and no recurrence on re-exposure. The sample is too small to draw any statistically significant conclusions, however, the results are mostly in line with those obtained from larger samples. Malta's incidence is towards the lower end of the reported range of 0.02% to 3.23%, but higher than that reported in centres trying to recognise NMS early and reduce risk factors. This suggests that Malta could benefit from trying to adopt such measures. Given Malta's small size, it would be relatively easy to disseminate such information. Keck et al describe the following measures for the early detection of NMS: i) increase in clinical awareness of the cardinal features of NMS; ii) treating neuroleptic induced extrapyramidal and autonomic side effects at their earliest emergence; iii) minimising risk factors such as the use of intramuscular neuroleptics. The other noteworthy point is the previously reported association of non-ketotic diabetic coma with NMS. This study, despite its comprehensive sample, failed to reveal any other reported cases. Nor has it been demonstrated that diabetics were at higher risk of developing NMS or its complications. It would be important to explore these possibilities further in future studies.

Keywords: *neuroleptic malignant syndrome, incidence, risk factors, morbidity, treatment*

Introduction

The Neuroleptic Malignant Syndrome (NMS) is an uncommon but potentially fatal idiosyncratic reaction to neuroleptics. It is characterised by a decreased level of consciousness, greatly increased muscle tone, and autonomic dysfunction including hyperpyrexia, labile hypertension, tachycardia, tachypnoea, diaphoresis and drooling. Laboratory abnormalities include greatly elevated creatine phosphokinase levels and leucocytosis.

The fact that all neuroleptics implicated in NMS share the property of D_2 dopamine receptor antagonism supports the involvement of dopamine in the pathogenesis of NMS. However the view that NMS results from dopamine blockade is simplistic as it fails to account for the rare occurrence of the syndrome and its unpredictable onset, even in patients with previous episodes.

Estimates of the *incidence* of NMS vary greatly and have ranged from 0.02% to 3.23% of neuroleptic-treated patients. These differences

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probably reflect differences in diagnostic criteria, survey techniques, patient populations, clinical settings and treatment practices.[1] Keck et al have found an NMS incidence of 0.15% in a prospective study of neuroleptic-treated patients.[2] In an earlier study at the same centre the incidence was 1.1%.[3] This decline was attributed to earlier recognition and reduction of risk factors. Pooling data from 16 studies of incidence of NMS in the literature, Caroff and Mann found 66 NMS cases among 33,720 neuroleptic-treated patients yielding an incidence of 0.2%.[4]

The demarcation between mild cases of NMS and the spectrum of more benign extrapyramidal effects of neuroleptics is very blurred. For this reason Pope et al developed *operational criteria for the diagnosis of NMS*.[5] According to these, the following three items are all required for *definite diagnosis*:

1. Hyperthermia: Oral temperature of at least 37.5 ^{0}C in absence of another known aetiology.

2. Severe extrapyramidal effects characterised by two or more of the following:
   - lead-pipe muscle rigidity
   - pronounced cog-wheeling
   - sialorrhoea
   - oculogyric crises
   - retrocollis
   - opistothonus
   - trismus
   - dysphagia
   - choreiform movements
   - dyskinetic movements
   - festinant gait
   - flexor-extensor posturing

3. Autonomic dysfunction characterized by two or more of the following:

   - hypertension (at least 20 mm rise in diastolic pressure above baseline)
   - tachycardia (at least 30 beats/ min above baseline)
   - tachypnoea (at least 25 resp/ min)
   - prominent diaphoresis
   - incontinence

In the case of retrospective diagnosis, if one of these three items has not been specifically documented, a *probable diagnosis* may be made if the other two criteria are clearly met and the patient displays one of the following characteristic signs:

- clouded consciousness as evidenced by delirium, mutism, stupor or coma
- leucocytosis (>15,000 WBC/cubic mm)
- serum creatine kinase level >300 U/L

Knowing the *risk factors* for NMS is very important in its prevention and Keck et al identified factors additional to dopamine blockade which are necessary to trigger an episode of NMS.[2,6] Risk factors can be either intrinsic to the patient, or related to the treatment used.

Neither *age* nor *sex* can be considered as risk factors, but a *past history of NMS* is a definite risk factor.[4]

NMS is not specific to any *neuropsychiatric diagnosis*, but amongst patients with NMS, there is a preponderance of affective disorders.[7,8] Affective disorder may reflect a state-dependant vulnerability to NMS. Most patients, prior to the NMS episode displayed significantly greater *psychomotor agitation*.[6,7] It is possible that this agitation represents undiagnosed akathisia, which might create a state-dependent predisposition to NMS.

Most patients with NMS present in a state of *dehydration*.[7] Dehydration may contribute to the development of NMS by increasing the effective concentration of neuroleptics in extracellular fluids. It may also be an effect of NMS rather than a predisposing cause, such dehydration being due to fever, diaphoresis an decreased fluid intake.

Nearly half of the patients with NMS suffer from an additional form of *brain pathology* or vulnerability apart from their psychiatric illness.[7] Although it has been suggested that NMS is not dose related, both Rosebush & Stewart, and Keck et al found the syndrome to occur with higher neuroleptic dosage albeit within the normal therapeutic range.[6,7]

Recent change in treatment also constitutes a definite risk factor for the development of NMS and this change can be either a recent onset or a recent increase of treatment.[7] It is not the increase in dosage, but the rate of dose increase, that is directly related to the development of NMS.[4,6]

In nearly 80% of the cases who developed NMS, the route of administration of treatment was *intramuscular*.[4,6,8] This risk increased tenfold if the neuroleptics were administered *without anti-parkinsonian agents*.[4]

Most studies report a significantly greater use of *lithium carbonate* in patients who develop NMS.[1,2,5] There is the possibility that neuroleptics combined with lithium carbonate are more liable to cause NMS than neuroleptics alone.

The *main complications* of NMS are rhabdomyolysis, respiratory complications, renal failure and finally death.

The mortality rate when only supportive measures are used is around 21%.[4] This falls to 10% when treatment more than mere supportive measures is used: for bromocriptine with other drugs, the mortality is 10.1%; for bromocriptine alone it is 7.8% and 10.3% for ECT.

About 25% of cases of NMS have *rhabdomyolysis* which can result in high levels of creatine phosphokinase and potassium, myoglobinuria and renal insufficiency. *Renal failure* develops in around one fourth of cases.[7,9] *Respiratory failure* develops in nearly 20% of cases. The cause of this is not clear but may involve aspiration, infection, shock and pulmonary emboli.[9] Other documented and less common complications of NMS are: myocardial infarction, pulmonary embolus, hepatic failure, disseminated intravascular coagulation, sepsis, deep vein thrombosis and E.coli fascitis[9,10]

In Malta, Pullicino et al reported two cases that developed cerebral infarction,[10] whilst Balzan and Cacciottolo reported one who developed diabetic coma as a complication of NMS.[11]

Very little information exists about the long term residual effects of NMS. Three out of the 24 patients in Rosebush et al's study had parkinsonian symptoms five months after the NMS episode.[7]

Most patients with NMS have psychiatric disorders that need psychotropic treatment raising the question of *re-treatment with neuroleptics*. In most cases neuroleptics can be re-introduced safely, but there is a significant risk of recurrence. An important variable when re-challenging with neuroleptics is the time that has elapsed since the episode, indeed there is a suggestion that two weeks may be the critical time lapse.[7] The potency of neuroleptics used in the re-challenge is the other important factor; a 30% NMS recurrence rate dropped to 15% when lower potency neuroleptics were used.[9]

Method and Sample

A retrospective sample of all known cases of NMS in Malta was reviewed. The sample was obtained by circulating all consultant psychiatrists, physicians, and ITU anaesthetists in Malta and Gozo, regarding possible cases of NMS under their care. All replied yielding thirteen possible cases and information about these cases was obtained by reviewing their case-records including whether they fulfilled the Pope criteria for NMS: twelve cases were thus identified of which ten fulfilled the Pope criteria for definite diagnosis of NMS, two patients for probable diagnosis and one did not, this latter thus being excluded from the study sample.

The incidence of NMS in neuroleptic-treated patients was then calculated for Malta's one psychiatric hospital, Mount Carmel Hospital. All in-patients diagnosed with NMS at Mount Carmel Hospital between the 1st January 1992 and the 31st December 1993 were collected. To calculate the incidence in neuroleptic-treated patients it was necessary to estimate how many patients were treated with neuroleptics during the same period. In line with Pope et al's study, one sixth of hospital admissions were reviewed and the proportion of patients on neuroleptics used to estimate the proportion on neuroleptics in the two year period.[5]

Results

The sample consisted of twelve patients, (seven males) with a mean age of 43.6 years (range 16-80). It was estimated that 596 (56.6%) of the 1053 patients admitted to Mount Carmel Hospital had been on neuroleptics for one week or more of which four developed NMS, yielding an incidence of 0.67%.

Of the total sample, one patient did not have any mental illness, neuroleptics having been prescribed as an anti-emetic. Four patients had affective disorder, three of them with psychotic features and one was also mentally retarded. The psychiatric diagnosis of the other patients were senile dementia in two cases, psychosis in a further three cases, one case of mental retardation and one of schizophrenia (Table I). One of the psychotic cases also had hydrocephalus. Two of the cases developed NMS during an episode of uncontrolled diabetes mellitus.

In nine cases, neuroleptics were prescribed by a psychiatrist, in one case by a physician and in an other by a surgeon. Eight patients developed

Clinical Sample

Case No	Primary Psychiatric Diagnosis	Change in regular treatment in last 7 days (CPZ mg equiv)	Total "stat" treatment in last 8 days (CPZ mg equiv)	Duration of NMS Hospitaliz-ation (days)	Treatment (additional to supportive measures)	Rechallenge (time lapse in days)	Rechallenge (treatment in CPZ mg equiv)
1		0-175		75	Bromocriptine		
2	Schizo-phrenia	222-225		86	Bromocriptine Levodopa Carbidopa		
3	Psychosis	0-150		105			
4	Psychotic Depression	40-1040		56	Levodopa Carbidopa	947	75
5	Manic Depressive Psychosis	75-75		41	Levodopa Diazepam	327	8
6	Senile Dementia	87-217		19	Levodopa Carbidopa		
7	None		Metoclopra -mide 10mg	4	Levodopa Procyclidine		
8	Acute Psychosis	0-150	1258	40	ECT		
9	Depressive Psychosis	1850-1850	1750	25	Diazepam	305	425
10	Mental Retardation	500-500	500	57	Bromocriptine Benserazide Levodopa	1	75
11	Mental Retardation with Manic Depressive Illness	850-2350		56	Bromocriptine Benserazide Levodopa	7	300
12	Senile Dementia	0-30	500	27	Levodopa Carbidopa		

Table I

NMS during the first fourteen days of their first exposure to neuroleptics, one patient had neuroleptics prescribed for the first time four months prior to the NMS episode with no other change in treatment, and the other two patients had been exposed to neuroleptics for two years but had an increase in treatment within the last ten days. Three patients were having their neuroleptics orally, eight both orally and intramuscularly and one patient had just a single dose of intramuscular neuroleptic treatment. Dosage change during the last seven days prior to the onset of NMS is shown in Table I. Only one patient was being treated concomitantly with lithium carbonate.

Prior to the onset of NMS, six patients were agitated and dehydration was present in four patients. None of the patients was treated by means of supportive measures alone. Treatments used were bromocriptine, levodopa either alone or with benserazide hydrochloride or with carbidopa, ECT, intravenous procyclidine hydrochloride and diazepam (Table I).

Only five patients had no complications of NMS. Renal impairment occurred in four patients and four patients needed assisted ventilation, one of them having lung collapse. Other complications of NMS were cerebral infarct in two cases, hypokinetic bowels in a further two cases and one case of deep vein thrombosis. There were no deaths due to NMS, however two patients have since died from other causes.

Five patients are known to have been re-prescribed neuroleptics after resolution of NMS. None of these developed NMS again (Table I).

Discussion

This study is limited in scope because it is retrospective and the sample is small, precluding meaningful statistical analysis. On the other hand, it constitutes the first attempt to study the incidence and factors related to the NMS as it occurs in Malta.

Notwithstanding the retrospective nature of the study, it is reasonable to assume, given Malta's small size and close knit medical community, that no known cases were missed. It is of course conceivable that the clinical diagnosis may have been missed in some instances, particularly in the elderly. The calculated incidence of 0.67% in this study shows the frequency of NMS in Malta to be towards the lower end of the 0.02 - 3.23% range reported in other studies, [1] but it is higher than the 0.15% reported in a centre which is trying to recognise NMS at an earlier stage and reduce its risk factors. [2]

As in most studies, dehydration, agitation, brain pathology and intramuscular neuroleptic administration were significant risk factors whilst the most common primary psychiatric diagnosis was affective disorder. In our study there was no significant correlation between the use of lithium carbonate and the development of NMS. The fact that ten patients had an increase in neuroleptic dosage during the seven days prior to the NMS episode supports this being an important NMS triggering factor. The finding that seven of the patients had, at no stage, received neuroleptics at dosages greater than 225 mg of Chlorpromazine equivalent, supports the view that it is the rate of the change of dosage rather than total dosage that is critical.

Since none of the patients were treated with supportive measures alone, no conclusions can be drawn about the different outcomes of supportive measures alone versus treatment consisting also of medication. Renal and respiratory complications were as common as in other studies. Thromboembolic complications and hypokinetic bowels also occurred. Two cases had uncontrolled diabetes mellitus and NMS occurring concominantly. The high incidence of diabetes mellitus in Malta makes this a relevant correlation.

In this study, none of the other patients developing NMS were diabetic. The proportion of the total sample exposed to the neuroleptics who were diabetic is not known but because of the high prevalence of diabetes in Malta i.e. 7.7%, [12] it can safely be assumed that a significant proportion were diabetic. Whether they constitute a sub-group at higher risk of developing NMS or its complications remains to be explored.

Further, while uncontrolled diabetes mellitus can be an NMS complication, it is also possible that the uncontrolled diabetic state can precipitate NMS, either by some direct effect or through resultant dehydration . Balzan and Cacciottolo,[11] suggest that uncontrolled diabetes mellitus together with dehydration may precipitate NMS in diabetic patients on neuroleptics and further that the hypermetabolic state in NMS may cause ketotic or non-ketotic diabetic coma in previously well controlled diabetics.

Two out of five patients re-challenged with

neuroleptics were within the two week suggested danger time interval after the resolution of the NMS episode. All patients re-challenged received less potent treatment than that prior to the NMS episode (Table I). This could be an important reason why none of the patients had further episodes of NMS.

Conclusions

Our sample of twelve patients is too small to draw any statistically significant conclusions, however the results are mostly in line with those obtained from larger samples. The incidence, which is higher than that reported in centres which are trying to recognise NMS at an earlier stage and reduce risk factors, suggests that Malta could benefit from trying to adopt such measures. Given Malta's small size it would be relatively easy to disseminate such information. Keck et al describe the following measures for the early detection of NMS [2]:

- Increasing clinical awareness of the cardinal features of NMS
- Treating neuroleptic induced extrapyramidal and autonomic side effects at their earliest emergence
- Minimizing risk factors such as use of intramuscular neuroleptics

The other noteworthy point is the previously reported association of non-ketotic diabetic coma with NMS.[11] Our study, despite its comprehensive sample, did not reveal any other unreported cases of comorbidity and has not demonstrated that diabetics were at higher risk of developing NMS or its complications. Nevertheless, it would be important to explore these possibilities further in future studies.

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