

THE NEUROLEPTIC MALIGNANT SYNDROME:

SIX CASE REPORTS

by

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May 1992

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INTRODUCTION

Neuroleptics - also known as major tranquillizers and antipsychotics - are among the most commonly prescribed types of medication in use today. While in psychiatric practice, they are used extensively in the treatment of psychotic disorders, they are also widely employed in general medical practice as anti emetics and as sedatives in the treatment of the acute brain syndromes that arise from certain organic disorders.

In the treatment of the psychoses, such as schizophrenia and major affective disorder, these agents are effective in the control of psychotic phenomena over a period of time. Their antipsychotic effect is attributed to their ability to block post-synaptic dopamine receptors in the various dopamine pathways in the brain. In addition, blockade of post synaptic dopamine receptors in the mesolimbic system may account for their ability to ameliorate the hyperdopaminergic state postulated as the underlying neurochemical dysfunction in schizophrenia. The same action in the nigrostriatal pathway may account for unwanted extrapyramidal effects that result from prolonged administration.

It is recognized that these explanations are simplistic, particularly in view of the complexity of molecular neurobiology and brain microstructure, evident in the recent explosion of scientific data in the field of the neurosciences.

Due to the non-specificity of many of the commonly prescribed neuroleptic agents, unwanted side effects may arise due to their action on various neurotransmitter systems. Occasionally a rare, but potentially life-threatening disorder may arise following neuroleptic exposure, which has been termed the neuroleptic malignant syndrome.

THE NEUROLEPTIC MALIGNANT SYNDROME [NMS]

The Neuroleptic malignant syndrome has been ascribed to an idiosyncratic reaction to neuroleptic drug therapy and may have a fatal outcome. The characteristic clinical features are generalized muscular rigidity, an altered state of consciousness, pyrexia and autonomic dysfunction which manifests as diaphoresis, tachycardia, tachypnoea and labile blood pressure. These features are associated with laboratory findings of a leukocytosis, a raised serum creatine phosphokinase and a low serum iron concentration.

The first description of the neuroleptic malignant syndrome was by French psychiatrists, Delay et al. in 1960. The paper appeared in the proceedings of the Société Médico-Psychologique for December 21, 1959, in a communication on the use of the then new drug Haloperidol and was described as a neurovegetative complication. The first description in English was by Delay and Deniker (1968), who used the term as a subheading in a chapter on drug-induced extrapyramidal

symptoms in the "Handbook of Clinical Neurology" (Eds. P.J. Winken & G.W. Bruyn, 1968).

In the English medical literature the first reference to Delay and Deniker's description of the syndrome was by Metzler (1973), who recognized it as a complication of treatment with depot fluphenazine enanthate and only four papers mentioned the term before 1980. Following Caroff's article in the North American literature entitled the "Neuroleptic Malignant Syndrome" (1980), it has gained increasing recognition.

CHAPTER ONE

LITERATURE REVIEW

Diagnostic and Conceptual Issues

The NMS was first thought to be a variant of drug fever in which hyperpyrexia, autonomic and other neurological abnormalities developed during the course of phenothiazine therapy.

Authors have put forward differing criteria for the identification of NMS. In 1985, Levenson categorized diagnostic criteria into major and minor manifestations to aid clinicians in the recognition of the syndrome.

Minor Manifestations

Tachycardia
 Labile Blood Pressure
 Altered Consciousness
 Diaphoresis
 Leukocytosis

Major Manifestations

Fever
 Muscular rigidity
 Elevated CPK

In his view, a positive diagnosis could only be made if the patient satisfied all the major criteria plus two of the minor criteria.

Other writers have favoured a spectrum concept of NMS. Fogel & Goldberg (1985), considered that NMS was a severe neuroleptic related neurotoxicity with various combinations of extrapyramidal, cortical and autonomic dysfunction. Guzé & Baxter (1985a), in their review of NMS, supported this concept. Whereas Cohen et al. (1985), suggested that the NMS may be an exaggerated form of neuroleptic induced parkinsonism, Conlon (1986), argued that NMS represented an extreme end of the spectrum of neuroleptic related toxic reactions. In their review article, Shalev and Munitz (1986), reported on so-called formes frustes, or atypical cases of the NMS, i.e. forms without fever or muscular rigidity.

On the other hand, Adityanjee (1988), challenged the validity of the spectrum concept of the disorder which had been based on anecdotal reports using arbitrary criteria for diagnosis. He claimed that the spectrum concept of NMS was an artefact of arbitrary definition and stated that NMS could not be diagnosed in the absence of any one of four ascribed clinical components, viz. muscular rigidity, an altered state of consciousness, hyperpyrexia [over 39°C] and autonomic dysfunction (tachycardia >90/min, respiratory rate >25/min, BP fluctuation of at least 20mm Hg in systolic pressure, excessive sweating and incontinence). Elevation of CPK and leukocytosis were considered as supportive features only, as

they are non-specific abnormalities which are associated with a number of other medical conditions.

In his often cited review, Caroff (1980), described NMS as having an abrupt, fulminant onset extending over 24 to 72 hours, whereas others have described a more insidious evolution of the symptoms (Bernstein, 1979; Chayasirisabhon, 1983; Coons, 1982; Ewert, 1983; Feibel, 1981).

INCIDENCE

It is inevitable that with the lack of consistency in defining the criteria for diagnosis, estimations of incidence have differed widely.

In an early review of NMS, Caroff (1980), estimated the incidence as 0.5 - 1.0% of all treatment episodes. Similar low figures were given by Shalev and Munitz (1986), who estimated incidence was 0.4%. From a prospective assessment of 679 patients, Pope, Keck et al. (1986), quoted an incidence of 1.4% for neuroleptic treated patients. A high incidence of 2.4% was cited by Addonizio (1986), from a retrospective chart analysis of 82 consecutive in-patients. Gelenberg et al. (1988), studied 2173 patients prospectively and identified only one patient who developed NMS out of 1470 given neuroleptics. The estimated incidence in this study was only 0.07%. In their prospective study of 9733 Chinese patients treated with neuroleptics Deng et al. (1990), found an incidence of 0.12%.

In a recent North American study, Keck et al. (1991), noted a significant decline in the frequency of the syndrome. In their study of 2695 neuroleptic treated patients, the frequency of occurrence of the syndrome was only 0.15% as compared to 1.4% in their earlier study. They suggested that the decline may be due to an increased awareness of risk factors and early intervention.

NMS AND ASSOCIATED FACTORS

Pharmacological agents:

Numerous reports have cited the most frequently used neuroleptics, the phenothiazines and butyrophenones as usually causing the NMS. However, all neuroleptics, including newer generation agents, have been implicated. These include sulpiride, clozapine, zuclopenthixol decanoate and metaclopramide. NMS has also been associated with the use of drugs which alter dopaminergic function. Toru et al. (1987) and Fujitake et al. (1984), reported cases of NMS following the abrupt cessation of dopamine agonists which were used to treat parkinsonism. The syndrome has also been recorded as being precipitated by several other drugs or drug combinations, which lower dopamine receptor activity. For example, Ritchie (1983), reported a case following an overdose of dothiepin and phenelzine. Eiser et al. (1982), described a case involving amitriptyline and thioridazine in therapeutic doses. NMS has also been associated with other pharmacologic

agents such as amoxapine (a new tricyclic antidepressant), carbamazepine, and lithium alone (Susman & Addonizio, 1987) or in combination with other medication.

NMS and Organic Brain Syndrome

Some reports have described NMS as occurring in various organic states treated with neuroleptic agents. These include Huntington's chorea (Burke et al. 1981), Alzheimer's disease (Addonizio, 1987; Finucane et al. 1988), mental retardation and AIDS (Breitbart et al. 1988).

NMS and Psychiatric Disorder

The NMS has been described as occurring predominantly in patients with psychotic disorders. Controversy exists concerning the association of NMS with schizophrenia or the affective disorders. In a recent prospective analysis of 24 cases of the NMS, Rosebush & Stewart (1989), noted a higher preponderance of affective disorder and a low incidence of schizophrenia in the cases presenting with NMS. Only one of the 20 patients in this study had a diagnosis of schizophrenia and that case also presented with an affective component to the schizophrenic disorder.

Addonizio (1986), also found a higher incidence of NMS in patients with a diagnosis of affective disorder. Of the 10 patients with diagnosed NMS, in this retrospective survey of

82 consecutive in-patients, seven had an affective disorder, one patient had a schizoaffective diagnosis and two patients were diagnosed as having schizophrenia. In view of these findings, both Rosebush and Addonizio have suggested that affective disorder may be a risk factor in the development of the NMS.

Sporadic cases reported in the literature also suggest an association of NMS with affective states, mainly bipolar affective disorder and manic states (Goekoop & Carbaat, 1982; Singh, 1981; Smith & Carter, 1984; Spring & Frankel, 1981; Town, 1982), but also depressive states (Sumiyashi et al. 1983).

It is interesting to note that there are cases where NMS has allegedly occurred in non-psychotic patients, for example, in patients with psychopathy, acute grief reaction and heroin addiction (Kellam, 1987). Two cases were reported as occurring in fit patients given neuroleptics as pre-operative medication (Konikoff et al. 1984; Moyes, 1973).

THE RELATIONSHIP OF NMS TO CATATONIA

Lethal catatonia ("Tödliche katatonie"), a term coined by Stauder (1934), was used to describe a life threatening febrile neuropsychiatric disorder, which was widely reported before the introduction of modern psychopharmacologic agents.

Symptoms of unexplained fulminating hyperpyrexia, widely described in the course of catatonia, have been described since the beginning of the nineteenth century, especially in the French literature as "délire aigue". Bell first described the syndrome in English as "Bell's mania" (Bell, 1849).

There has been a notable decline in the reporting of catatonia in the post neuroleptic era, although occasional cases have been described in the European and Asian literature. Mann (1986), in his review of lethal catatonia, identified 292 cases reported since 1960. He suggested that catatonia is a 'syndrome' rather than a specific disease and may occur during the course of either an organic or functional disorder. He suggested that it is a non-specific response of the CNS associated with various neurological, medical and psychiatric syndromes, in brief, it is a syndrome with varied aetiologies.

The clinical entity recognised as the NMS closely resembles advanced catatonia. Several authors have observed that the clinical features of the two syndromes are indistinguishable (Fricchione, 1983; Meltzer, 1973; Weinburger, 1977). Mann (1986), identified 65 patients (22%) in his series of 292 patients with catatonia where the clinical phenomenology appeared to be equally consistent with a diagnosis of NMS. It is interesting to note that these patients were diagnosed as lethal catatonia only after neuroleptic exposure.

Several writers have proposed that the neuroleptic malignant syndrome represents a neuroleptic-induced, toxic or iatrogenic

form of lethal catatonia (Bourgeois, 1981; Fricchione, 1985; Gabris, 1983; Kick, 1981).

In his overview of NMS and its relationship to catatonia, Fricchione (1985), presented the hypothesis that 'neuroleptic induced catatonia' and so-called 'psychogenic catatonia' may share a common pathophysiological pathway. He suggested that 'neuroleptic induced catatonia' may be analogous to the potentially lethal variant known as the NMS and likewise such an analogous relationship can be said to exist between so called benign "psychogenic catatonia" which, in its more severe form, may become a lethal variant of catatonia.

The clinical features of catatonia include mutism, posturing, stereotypy, waxy flexibility, negativism, catalepsy, incoherent speech, an altered state of consciousness which may become a profound stupor, and psychomotor agitation. These features may be associated with somatic disturbance such as tachycardia, sweating, tachypnoea, labile blood pressure and fever. In the lethal variant, extreme agitation may lead to exhaustion, dehydration and hyperthermia with coma, cardiovascular collapse and death. In many cases skeletal musculature has been described as flaccid in the terminal stupor whereas other cases have displayed muscular rigidity. Stauder (1934), noted that each of his 27 patients experienced a stuporous period following psychomotor agitation in which patients in the terminal phase of illness would lie with their "musculature tensed" and "bizarre posturing" which lasted two

to four days and ended in death. Early literature refers to cases of lethal catatonia in which the entire clinical course was characterized by stupor and rigidity unassociated with hyperactivity (Bell, 1849; Tolsma, 1956).

Some authors claim that the NMS has often gone unrecognized as cases involving neuroleptic exposure were sometimes attributed to lethal catatonia (Lancet, 1984; Zubenko, 1983). The difficulties in distinguishing between the two syndromes have been cited by several writers (Caroff, 1980; Powers, 1976; Weinberger & Kelley, 1977). There is ongoing debate as to whether catatonia and NMS should be differentiated. Castillo et al. (1988) and Fleishhacker (1990), argued that there is a need to differentiate the two syndromes for the purpose of treatment, since patients with catatonia may require neuroleptics or ECT, whereas patients with NMS require the immediate cessation of neuroleptic medication and the administration of dopaminergic agents.

Kellam (1987), in an excellent review of the NMS, suggested that in some cases of apparent NMS, the underlying catatonic state was probably overlooked as attention was focused on the pathogenicity of the neuroleptic agent. Kellam states as follows: "this raises the question as to whether catatonia may itself sometimes become a life threatening condition and whether in some cases of apparent NMS, neuroleptics are not pathogenic".

AETIOPATHOGENESIS

The two major competing theories attempting to explain NMS are a central dopaminergic blockade versus a direct toxic (hypermetabolic) effect on skeletal muscle. Burke et al. (1981), described a patient with Huntington's Chorea, who developed NMS while taking alpha methyltyrosine and tetrabenazine; the former inhibits dopamine synthesis, while the latter depletes CNS catecholamines by interfering with their storage. They suggested that NMS is caused by dopamine depletion or blockade resulting in derangement of central thermoregulation. Henderson and Wooton (1981), supported this hypothesis, citing a patient with Parkinson's disease and chronic psychosis who developed NMS when dopaminergic agents Levodopa carbidopa and amantadine were withdrawn. The patient was also receiving lithium and haloperidol. A similar case was reported by Toru et al. (1981), where a patient with Parkinson's disease developed NMS when l-dopa/carbidopa and amantadine were abruptly discontinued. The patient had no neuroleptic exposure.

Fricchione (1985), postulated that NMS is secondary to dopamine blockade in the mesostriatum, which is responsible for the motor disorder in the preoptic anterior nuclei of hypothalamus accounting for hyperthermia, and in the brain stem which results in mutism.

Rosebush and Mazurek (1991), postulated that the acute phase reaction may have a role in NMS. In their study of 26 cases of NMS they noted a high occurrence (96%) of low serum iron concentration during the active phase of the illness, which may have had some bearing on striatal dopamine receptor function.

Nisijima and Ishiguro (1990), in their study of CSF monamine metabolism in eight cases of NMS, found that the levels of homovanillic acid (HVA) were significantly low in patients with NMS compared to controls in the active phase and after recovery. They claimed that this supported the central dopamine blockade theory of NMS pathophysiology. They also suggested that there may be decreased dopamine metabolism in patients susceptible to NMS.

They also reported significantly decreased levels of 5-HIAA in patients with active NMS and after recovery, compared to the control group, suggesting a relationship between development of NMS and a disturbance of serotonin metabolism. The levels of nor adrenalin (NA) in patients with active NMS were significantly higher than in normal subjects, and were within the normal range after recovery. The levels of MHPG also tended to rise in patients with active NMS, compared with the levels during recovery. They postulated that this finding was a result of increased sympathetic nervous system activity and may well reflect the physical stress caused by NMS. They commented that a similar response is also seen in other

conditions such as malignant hyperthermia, head injury and subarachnoid haemorrhage.

Several investigators have suggested that NMS and malignant hyperthermia (MH) may share a common pathogenetic mechanism (Caroff, 1980; Levenson, 1985; Shalev & Munitz, 1986). Clinically, MH and NMS are similar, both presenting as hypermetabolic episodes, usually with pronounced muscle rigidity, rhabdomyolysis and hyperthermia. Laboratory evidence of MH-susceptibility in six NMS patients provided support for the hypothesis put forward by Caroff et al. (1987), that the development of muscular rigidity in NMS is a function of similar skeletal muscle abnormalities as might be present in MH susceptible patients, which may be triggered by neuroleptics.

DIFFERENTIAL DIAGNOSIS

Investigators have noted the similarity in the clinical features of the NMS and other disorders such as heat stroke, malignant hyperthermia, drug reactions such as anticholinergic toxicity, MAOI toxicity or hyperthermic reactions to synthetic narcotics or tricyclics when given together with MAOI's. An important factor to consider in differential diagnosis is the occurrence of a febrile medical illness in the course of neuroleptic therapy. Levinson and Simpson (1986), observed that out of 39 reported cases of NMS, 16 of these patients with features of NMS also had medical

problems that occurred during the course of neuroleptic therapy which could have accounted for the presence of fever.

Several features of NMS are seen in anticholinergic toxicity, i.e. fever, delirium, tachycardia and a history of psychotropic medication. However, anticholinergic toxicity is characterized by a lack of sweating rather than diaphoresis, and a low blood pressure versus a labile or increased BP, urinary retention instead of incontinence. The laboratory findings of leukocytosis and clinical finding of muscular rigidity are usually absent.

Several writers (Levenson, 1985; Levinson (1986); Fricchione, 1985; Rosebush, 1989) included catatonia as part of the differential diagnosis, and emphasized the need to differentiate the syndrome from the NMS.

Patients taking neuroleptics are at increased risk of heat stroke which may be related to the inhibition of sweating secondary to anticholinergic medications. This syndrome may resemble NMS, particularly if there are associated extrapyramidal side effects. Distinguishing features are the absence of sweating, a low blood pressure and normal muscle enzymes and white cell count.

PREDISPOSING/RISK FACTORS FOR THE DEVELOPMENT OF THE NMS

Innumerable patients are treated with neuroleptic and other psychotropic medication with no major sequelae. The factors predisposing a small percentage of patients to the NMS are unknown, but, due to the potential lethal outcome of this syndrome, it is vital to identify possible risk factors.

Addonizio (1987), in his review and analysis of 115 cases of NMS, was unable to identify any significant factors contributing to the development of the NMS. He concluded that case reports alone would not provide an answer to the NMS but that controlled prospective studies might reveal the underlying pathophysiological mechanism. More recent studies have linked NMS to several possible preconditions:

From the findings in their prospective study of 26 episodes of NMS, Rosebush & Stewart (1989), listed the following features as possible predisposing factors:

- an increasing dosage of neuroleptics or initial introduction to neuroleptics in a vulnerable patient.
- agitation and restlessness.
- dehydration.
- a diagnosis of affective disorder.
- concurrent use of medication such as lithium or antidepressants.
- other forms of organic brain pathology.

Keck and Pope (1989), found significant differences between a group of patients with NMS and a group of neuroleptic-treated controls. Based on these findings, they suggested the following as possible risk factors for the NMS:

- psychomotor agitation,
- rapid neuroleptisation,
- an affective disorder.

Harsh (1987), identified dehydration as a possible risk factor in a study of nine patients with NMS. It is interesting to note that Levinson and Simpson (1986), in their retrospective survey of 39 patients with extrapyramidal side effects and fever noted that 24 patients were agitated prior to the onset of symptoms and that dehydration was present in 12 of them. In their study of Japanese patients, Itoh et al. (1977), commented on the incidence of agitation before NMS.

Otani et al. (1991), suggested that the predisposition to NMS may be genetically transmitted, based on a study of a Japanese family where a mother and her two daughters all experienced NMS on therapeutic dosage of neuroleptics.

SPECIAL INVESTIGATIONS

Investigative findings are usually non-specific and are useful in excluding or confirming the clinical diagnosis of NMS. The laboratory findings commonly associated with NMS are:

- raised serum creatine phosphokinase
- leukocytosis
- low serum iron concentration.

The iso enzyme phosphocreatine kinase (CPK mm) level is often elevated and may exceed 30,000 I.U./L reflecting myonecrosis. Rhabdomyolysis with associated myoglobinuria may lead to acute renal failure in severe cases of NMS. The transaminases, lactic dehydrogenase and alkaline phosphatase may also be raised. There is uncertainty as to whether these enzymes are from liver or muscle.

The role of serum iron, CPK and leukocytosis in NMS will be discussed further in chapter three.

MANAGEMENT OF THE NMS

Pharmacological Intervention

Dantrolene/Bromocriptine:

Although various treatments have been proposed, most clinicians adhere to basic principles such as the immediate cessation of neuroleptic therapy and supportive treatment. There are conflicting accounts in the literature as to the efficacy of pharmacological intervention with dopamine agonists such as Bromocriptine and/or skeletal muscle relaxants such as dantrolene. Levenson (1985), found that cases of NMS treated with supportive measures only, did not differ in course of illness from those who had received bromocriptine and/or dantrolene.

Rosebush and Stewart (1991) analyzed 55 cases and found that patients treated with bromocriptine and/or dantrolene had signs of NMS for a mean of 9.9 days compared with 6-8 days in those receiving supportive care only. However, they could not exclude the possibility that the drug treated patients may have been more seriously ill than those treated with supportive measures only. Deng et al. (1991), found bromocriptine and dantrolene of little use in their patients.

Conversely, Rosenberg and Green (1989), in their review of 64 treated cases from the world literature, found that with supportive measures only, the mean time for a clinical

response was 6-8 days while the addition of dantrolene reduced this to 1-2 days and bromocriptine to one day.

Benzodiazepines

Several investigators have reported transient relief of symptoms with benzodiazepines (Burke et al. 1981; Fricchione, 1983; Lew & Tollefson, 1983; Morris, 1980). Rosebush and Stewart (1989), observed that patients needed benzodiazepines to ease discomfort and to decrease the hyperadrenergic state associated with the syndrome.

The Use of Electroconvulsive Therapy (ECT)

Hermesh et al. (1988), recommended ECT as a treatment option in the active phase of NMS, since four cases had a successful outcome. They concluded that due to the postulated ability of ECT to increase post synaptic receptor sensitivity to dopamine, this might explain its beneficial effect in NMS.

Adityanjee (1987), challenged the recommendation of Hermesh et al. (1988), in the use of ECT as a specific treatment modality for NMS and cited two cases where cardiac arrest occurred during ECT, which resulted in permanent brain damage in one case. He concluded that the use of ECT is controversial and advocated the use of safer treatments such as bromocriptine and dantrolene.

In a review of 734 published cases of NMS, Davis et al. (1991), found that 48 cases were treated with ECT either during or shortly after an episode of NMS. They compared these with a group of controls who received no specific treatment and concluded that ECT is probably safe in the treatment of NMS since no serious unexpected events occurred with its use during an episode, provided neuroleptics had been stopped.

TREATMENT OF THE UNDERLYING PSYCHOSIS

Challenge with Neuroleptics

The probability of recurrence of NMS after recovery when challenged by further neuroleptic treatment was discussed by Wells et al. (1988). Of the 24 patients challenged, six showed a relapse of symptoms. The investigators noted that a 'drug holiday' of more than five days before challenge with a further dose of neuroleptics, was related to a reduced likelihood of recurrence.

They concluded that further neuroleptic treatment was an acceptable risk, if further treatment was needed. Rosebush et al. (1989), also noted that a period of not less than two weeks after NMS before challenge or rechallenge was associated with success.

OUTCOME OF THE NEUROLEPTIC MALIGNANT SYNDROME

Delay and Deniker (1968), characterized the syndrome as 'malignant' due to a possible fatal outcome. Caroff (1980), in a review of the early literature, cited a mortality rate of 20%. Levinson and Simpson (1986), in an analysis of 39 cases with extrapyramidal symptoms and fever, recorded three fatalities, which represented a mortality rate of 7,7%. Each death could be explained by recognisable medical complications rather than by a specifically neuroleptic induced mechanism.

In a review of 115 cases of NMS, Addonizio et al. (1987), found a mortality rate of 11%. Death resulted from medical complications that arose during the course of NMS such as pneumonia, renal failure, sepsis and pulmonary embolism.

There were no fatalities in a prospective study of nine Chinese patients (Deng et al. 1990). Likewise, there were no fatalities and few sequelae in a series of 24 episodes of NMS despite the fact that all patients were extremely ill (Rosebush and Stewart, 1989).

CONCLUSION

It is clearly evident in this review of recent literature that many inconsistencies and uncertainties exist about the neuroleptic malignant syndrome, with particular regard to pathophysiology, diagnostic criteria, incidence, risk factors, interventions and the relationship of NMS to catatonia.

CHAPTER TWO

METHODOLOGY

A series of six consecutive cases who were admitted to the psychiatric emergency unit at Groote Schuur Hospital between May 1989 and November 1990 are described.

Following the emergence of symptoms of the neuroleptic malignant syndrome, the patients were admitted to a medical ward under combined specialist management, which included a physician, a psychiatrist and a neurologist, supplemented by competent nursing.

CASE ONE

A 25 year old married Coloured female was admitted to the psychiatric emergency unit with a history of sudden onset of bizarre behaviour described as episodic mutism and withdrawal alternating with restlessness and incoherent speech. The patient had complained of feeling unwell for several days prior to onset of the behaviour change.

On examination: She was noted to be pyrexial with a temperature of 37.6° , pulse rate 76/min, BP 130/70.

The patient was disorientated and agitated. She appeared perplexed and fearful and was incoherent: in addition there was posturing and waxy flexibility of the extremities.

A differential diagnosis was made of delirious state or a dissociative disorder: she was admitted to a medical ward for further investigation. She required sedation on admission and was given Etomine 80mg i.v.i. and diazepam 10mg. i.v.i. Within 72 hours the patient became progressively more stuporous: this obtunded state alternated with restlessness and agitation. As she became more withdrawn and stuporous she required naso-gastric feeding and urinary catheterization.

Investigations were as follows:

CXR: Mild patchy consolidation left lower lobe ? due to aspiration.

EEG: No abnormality

L.P. : No abnormality of CSF

CT scan of head : Normal

Electrolytes: No abnormality

CPK: 11,000 I.U./L (Normal Range 50 to 110 I.U./L.)

LDH: 579 units/L (Normal Range 175 to 350 units/L)

AST: 56 units/L (Normal Range 7 to 25 units/L)

Alk Phos: 87 I.U./L (Normal Range 30 to 70 I.U./L)

FBC: White cell count $19 \times 10^9/l$.

Toxicology Screen: Non contributory

MSU: 3+ proteinuria (no myoglobinuria)

Collagen screen : Normal

Blood Culture : Negative

V.D.R.L.: Negative

Thyroid Function: Normal

Course in Hospital

By day 5 the patient was very ill and examination showed:
Temp. 39°C: PR 130/min: RR 30/min: Intermittent diaphoresis.
MSE: Profound stupor

Neurological: Generalized muscular rigidity (lead pipe) associated with episodic involuntary movements involving all four extremities. At times she was noted to have a mild tremor of the extremities, pill rolling of both wrists and a coarse tremor of the tongue. Both glabellar tap and palmar-mental reflex were positive. Tendon jerks were present but asymmetrical (L) to (R) Plantar reflexes.

By day 7 her physical state had improved, but she remained in a markedly catatonic state. She was given Diazepam 10mg. i.v. with dramatic response in that she was able to give a coherent account of herself. She was orientated for person and place but not time. She gave information about her husband and baby and about her work at the factory. Several hours following the diazepam interview she again lapsed into a mute and catatonic state, refusing to feed herself and became incontinent of urine. A low grade temperature, tachycardia, diaphoresis and neurological signs persisted.

A provisional differential diagnosis was made of:

- ? Neuroleptic malignant syndrome
- ? Viral encephalopathy and delirium.

Due to her obtunded mental state it was decided to proceed with ECT, which was given on day 9. Slight improvement was observed as she became more alert and was able to feed herself, although she remained withdrawn and uncommunicative.

On day 14 she suddenly became agitated and was immediately given Etomine 40mg i.v. and Haloperidol 10mg. i.v. Within 24 hours she was noted to have marked generalized muscular rigidity but she did not manifest any other clinical or laboratory abnormalities to indicate a relapse of the neuroleptic malignant syndrome.

The clinical features of NMS resolved within 14 days but due to persistence of a psychotic mental state she was referred for admission to Lentegour Psychiatric Hospital for further management of her psychotic state which was characterized by aggressive and irrational behaviour, nihilistic and persecutory delusions such as "I don't have a heart any more", "My boyfriend is going to kill the sister in the ward", "My mother says I'm too black to know what is going on". She was treated with clozapine 50mg. b.d. from Day 17 with no recurrence of NMS.

Psychosocial Background

During her admission to GSH collateral information was obtained from her mother who stated that her daughter, a factory supervisor, recently married into a family of whom her own family strongly disapproved. At one stage she was disowned by the family for making the decision to marry. She had a baby of 6/12 and lived with her husband in the home of her in-laws. She seldom saw her mother. Her husband was reported to be a womaniser; he spent little time with his wife and baby. The patient was always a quiet, hard working and competent person. There was no previous psychiatric history, although she was a slow learner at school and left after completing Standard 4 at the age of 16. No past medical history.

Family History:

Father's uncle had an admission to a mental institution, diagnosis unknown.

Course in Hospital at Lentegueur

The patient was treated with Clozapine 25mg b.d. and after six weeks she made a sudden and dramatic recovery and was discharged home without medication.

Follow-up:

The patient has had no further problems at three years follow-up and functions well as mother, wife and as supervisor

in a factory. There are no residual features of a psychotic disorder.

Final Diagnosis DSMIII-R

Neuroleptic malignant syndrome in a patient presenting with a catatonic syndrome followed by a brief atypical paranoid psychosis.

Axis I Catatonia/Atypical paranoid psychosis

Axis II Deferred

Axis III Neuroleptic malignant syndrome

Axis IV -

Axis V -

CASE TWO

A 20 year old Xhosa male was admitted to the emergency unit on 14.6.1989. The history given by his mother stated that he was unemployed and lived with her in Guguletu. He had been feeling unwell for a period of two weeks when suddenly four days before she brought him to hospital he became withdrawn, mute, stared into space and remained motionless for hours. At times he would become acutely fearful and agitated and ran around the home. He was brought to hospital in a state of psychomotor agitation and required sedation on admission. He was given Etomine 80mg. i.v. and Diazepam 10mg. iv.

On examination after sedation:

Pulse rate 140/min: BP 120/80: Temp. 37.7°C.

There was evidence of mild dehydration. A diagnosis of strange behaviour ? dissociative disorder was made in medical emergency and on day 2 he was referred for a psychiatric opinion.

On examination in psychiatric emergency unit:

Labile pulse rate 80 to 130/min: Labile BP 160/110 to 120/70: Temp : 37.5°C: Intermittent diaphoresis.

On neurological examination he had waxy flexibility, posturing, and an obtunded mental state.

On day 3 he suddenly became agitated and was given Etomine 80mg. i.v. and Diazepam 10mg. i.v. Thereafter he became profoundly stuporous with marked autonomic instability, a low grade pyrexia of 37.8°, generalized muscular rigidity, diaphoresis.

Provisional Diagnosis:

Neuroleptic malignant syndrome.

Investigations

	Day 2	3	4	5	6	7	8	
Na	148	142	-	137	-	-	-	mmol/l
Ur	11.4	8.6	-	5.0	-	-	-	mmol/l
CPK(mm)	300	369	-	1086	670	-	205	I.U./l

CXR NAD

LP: NAD

EEG: Normal 10 hertz alpha background

FBC: White cell count $7.5 \times 10^9/L$

CT: Normal

Toxicology Screen: NAD

MSU : NAD

Thyroid: NAD

VDRL : Negative

Course in Hospital

The patient required i.v. fluids and naso-gastric feeding to correct and maintain hydration and nutrition. He was treated with supportive measures only and was given Diazepam 10mg. i.v. for sedation when needed. He remained unresponsive and stuporous until day 5, when he suddenly improved and was more alert and communicative and was able to feed himself. Nasogastric feeding was discontinued. However, the patient remained restless and psychotic and a continued problem of containment.

On day 6 he was given a small test dose of Clozapine (50mg.) with no ill effect. On day 10 he was transferred to Valkenberg Psychiatric Hospital for further management of his abnormal behaviour. At the time of referral he had persistent severe extrapyramidal signs and mild fluctuations of pulse and BP.

Course in Valkenberg

He was treated with small doses of clozapine and made an uneventful recovery after six weeks.

Psychosocial Background

There was little information about this patient, but the mother stated that he had worked at S.A. Breweries until one month before admission to hospital, when he suddenly lost his job. He did not abuse substances, namely alcohol, dagga, mandrax. He had no previous psychiatric history, nor had he been taking any medication. He had sustained a serious head injury with concussion at age six, but there had been no sequelae. He had a Standard 7 education.

Family History:

Mother had recently been discharged from Valkenberg with a first psychotic breakdown at 40 years. She was taking chlorpromazine 100mg. daily. Diagnosis: ? Schizophrenia.

Final Diagnosis

Neuroleptic malignant syndrome in a patient presenting with catatonia followed by an atypical psychosis.

Axis I Catatonia/

 Atypical paranoid psychosis

Axis II -

Axis III Neuroleptic Malignant Syndrome

Axis IV -

Axis V -

CASE THREE

A 20 year old Xhosa male was admitted to the emergency unit at GSH on 9.6.1981. His father gave the history that the patient got up to go to work the day before admission and complained that "something was biting his legs". During the day he became quiet and withdrawn and later was noted to be mute, immobile and uncommunicative. This behaviour was followed by the sudden onset of an acutely agitated state at which stage his family restrained him and brought him to hospital.

Examination on admission:

Temp : 36.4°: Pulse rate: 88/min: BP 140/90.

He was catatonic, displaying waxy flexibility, posturing, mutism and negativism.

Sedation was given for an episode of agitation following the initial mute state - Etomine 80mg. i.v.i. and Diazepam 10mg. i.v.i.

Examination day 2:

Temp. 37.5°: Pulse rate 120/min: BP 160/100.

Neurological examination: Generalized increased muscular tone.

MSE : Mute and unresponsive.

Examination day 3:

Persistent tachycardia and labile BP: Temp. 38^o: Urinary incontinence. Generalized muscular rigidity and episodic protrusion of the tongue.

Mental State examination: Mute and unresponsive.

No evidence of dehydration.

Investigations:

CEUG : NAD

CxR : NAD

CSF : NAD

MSU : NAD

EEG : Normal

CT of head: Normal

Blood culture: Negative

Toxicology Screen: NAD

VDRL : Negative

HIV : Negative

FBC : White cell count = $6.88 \times 10^9/L$

CPK (mm) : 1104 I.U./L

Provisional diagnosis: In view of the clinical features and elevated CPK (mm) a diagnosis of Neuroleptic malignant syndrome was made.

Course in Hospital and management

The patient remained stuporous and rigid from day 2 - 10. He continued to have a persistent tachycardia, fluctuating BP, Temp. 38° and intermittent diaphoresis. On day 5 he was given Atendol and Adalat in an attempt to control his autonomic signs, but there was little response.

Throughout the illness the patient was maintained on i.v. fluids and nasogastric feeding.

On day 9 his CPK had dropped to 387 I.U./L and there was some improvement in his general condition. He suddenly became restless at night and was inadvertently sedated with haloperidol 5mg. i.v.

NB: This was followed by a rise in CPK to 1095 I.U./L on day 10 and increased muscular rigidity. Ongoing management consisted of supportive measures only and diazepam 10mg. i.v. was given to control restless behaviour when necessary.

Neurological Examination:

In addition to generalized muscular rigidity which had a lead pipe quality, upper motor neurone signs developed in both lower limbs. Knee and ankle jerks were markedly increased and there was sustained ankle clonus bilaterally. Plantar reflexes ↑.

By day 12 the acute illness had settled but the catatonic state persisted. He was given ECT x 2 treatments and there was a gradual improvement in his mental state and mobility. By day 17 it was evident that he had an abnormal mental state with features of hypomania. It was observed that occasional episodes of autonomic instability and sweating persisted, but CPK returned to normal levels and he remained afebrile. In addition, there was residual parkinsonism, hyper reflexia of the lower limbs and generalized increased muscle tone.

At this stage the patient was referred to Valkenberg Hospital for further management of his hypomanic state. He was treated with small doses of clozapine and discharged after six weeks. He has remained well at follow up visits and is functioning normally in his occupation as a garbage collector.

Psychosocial History and Past History

The information given by the father stated that the patient was a garbage collector in Khayelitsha and was presently residing with the father.

There was no history of drug/alcohol abuse, and no history of fits or head trauma or previous medical history of note. There were no recent stressors, although the patient had always been a worrier and a poor achiever with a Standard 4 education. There was no family history of psychiatric illness.

Final Diagnosis

Neuroleptic malignant syndrome in a patient presenting with catatonia followed by hypomania.

Axis I Catatonia/first manic episode/Bipolar affective disorder

Axis II -

Axis III Neuroleptic Malignant Syndrome

Axis IV -

Axis V -

CASE FOUR

A 48 year old Coloured female was admitted to the medical emergency unit at GSH on 6.8.1989 from Lentegeur Hospital with a diagnosis of "aphasia" ? due to cerebral vascular accident (CVA). The patient was a known non-insulin dependent diabetic of late onset. On admission a diagnosis of hysteria was also considered and she was referred to the psychiatric emergency unit for further assessment. She was noted to be mute and immobile and at times restless with incoherent speech. She was given chlorpromazine 100mg. intramuscularly for agitation and referred back to Lentegeur.

She was sent back to GSH 24 hours later due to deterioration in her condition. A provisional diagnosis of an alcohol withdrawal state was suggested.

On examination:

Temp. 38⁰: BP 160/120: Pulse Rate 90/min.: Resp. rate.
20/min: Sweating.

Neurological: Mild coarse tremor noted of upper extremities
associated with generalized muscular rigidity.

Mental state was stuporous.

Patient appeared mildly dehydrated.

Investigation:

CEUG : Confirmed mild dehydration

Glucose: Mild elevation of blood glucose

FBC : WCC 14 x 10⁹/L

LP : NAD

CxR : NAD

MSU : NAD

VDRL : Negative

Blood culture: NAD

Toxicology: NAD

CPKmm: 622 I.U./L

LDH : Normal

EEG : Normal

CT scan : Normal

Provisional Diagnosis:

Neuroleptic malignant syndrome

Course in Hospital

For the following eight days after admission the patient had a fluctuating temperature up to 38.5°: pulse rate 120/min: RR 24/min: BP 170/120.

There was intermittent diaphoresis and marked generalized muscular rigidity (lead pipe).

Mental state stuporous and unresponsive.

On day 8 the patient was given bromocriptine 5mg. t.i.d. with little effect. The drug was discontinued on day 11. The patient was treated by supportive measures only with nasogastric feeding and intravenous lines. Glucozide 80mg. was administered 2 x daily via N/G tube. By day 12 there was a marked improvement in the patient's physical condition and mental state. The support lines were discontinued as the patient was able to feed herself. The generalized muscular rigidity was still noted by day 15, but the patient was mobile. By day 20 she had fully recovered from the NMS, but her mental state was noted to be depressed. She was apathetic, and cried frequently. She was given ECT x 3 for depression over the next ten days with little improvement noted.

On day 30 she was referred to Lentegour Hospital for further management of a depressive disorder. She was treated with amitriptyline and discharged after one month.

She remained well at follow up after two years, although complained of residual pain in the legs and feet following the illness. She continued to take medication for her diabetes and mild hypertension but discontinued antidepressants.

Past History and Psychosocial History

A neighbour gave collateral that the patient was a cleaner in a laundry. On the day of onset of the illness she had gone to work as usual when she suddenly became mute and unresponsive and was rushed to Lentegour Hospital.

There was no history of past psychiatric illness. There were no apparent stress factors except that her husband was unfaithful and she was often left alone at home. No past medical history except niddus and essential hypertension.

Final Diagnosis

Axis I Catatonia
 Major depressive episode
 Axis II -
 Axis III Neuroleptic Malignant Syndrome/Hypertension/Diabetes
 Mellitus
 Axis IV -
 Axis V -

CASE FIVE

A 33 year old Coloured female was admitted to the medical emergency unit from Piketberg on 11.10.89, with a one-day history of sudden onset of a mute and immobile state. She had been well previously and there was no past psychiatric history. In hospital she became acutely agitated and incontinent and was sedated with Etomine 80mg. intravenously. She was assessed in the psychiatric emergency unit as 'manic' and referred to Lentegeur hospital for admission. Two days later she was referred back to GSH in a stuporous and pyrexial condition with bizarre involuntary movements of the head and neck and facial muscles. It was noted that in Lentegeur she had received chlorpromazine 100mg. intramuscularly on two occasions.

On examination:

Temp. 38,5^o: pulse 110/min: BP 130/80.

Neurological: Generalized muscular rigidity.

Episodic dystonic movement as described above.

Mental state: Stuporous and unresponsive.

Mild dehydration.

Investigations:

FBC : WCC 16,62 x 10⁹/L

Enzymes: CPK 1662 I.U./L

ALT 190 units/L

AST 127 units/L

CEUG: Na 157 mmol/l
K 4,8 mmol/l
Creatinine 130 umol/l
Urea 20,8 mmol/l
LDH 786 units/L

EEG Generalized non-specific slowing

CT Head: Normal

LP NAD

MSU NAD

CxR NAD

Toxicology negative

Screen:

VDRL Positive

CSF FTA Negative

Course in Hospital

The patient continued to manifest a fluctuating temperature, autonomic instability, intermittent diaphoresis, stuporous mental state and persistent generalized muscular rigidity with bizarre movement until day 10, when she began to improve gradually.

She was managed with supportive measures and diazepam 5mg. b.d. When she had recovered from the acute illness there was no evidence of a residual psychiatric disorder. She was discharged home 21 days after admission.

Psychosocial Background

The patient was the wife of a farm labourer in the Piketberg area. She reportedly had an argument with her father the day before onset of the illness. There was no history of drug taking, alcohol, head injury or fits. There was no family history of psychiatric disorder.

Follow-up

The patient remained well at 3 years follow up. There has been no relapse of illness.

Final Diagnosis

Axis I Catatonia
Axis II -
Axis III Neuroleptic Malignant Syndrome
Axis IV -
Axis V -

CASE REPORT 6

Episode One

A 33-year old woman of Malaysian origin was admitted to the psychiatric emergency unit in a profoundly stuporous and unresponsive state. On examination she was pyrexial, temperature 37,8 C, pulse rate 150/min, B.P. 150/100,

respiratory rate 36/minute. She had marked intermittent diaphoresis and generalized muscular rigidity. There was no evidence of dehydration. On investigation she had a raised CPK, (1185/IU/L) and a raised white cell count ($16,9 \times 10^9 / l$). Toxicology screen, chest x-ray, lumbar puncture, blood culture, MSU, EEG, C-T scan were normal.

Collateral information obtained from the patient's family stated that she had been taking chlorpromazine, 25mg at night, one month before admission. During that period she had developed increasing stiffness of the limbs and had become progressively withdrawn, fearful and agitated. Three days before admission she had deteriorated into a mute, immobile and rigid state. Because the presenting clinical picture emerged during the administration of chlorpromazine, a working diagnosis of NMS was made. The stuporous mental state and muscular rigidity responded dramatically to the administration of diazepam (20mg i.v.) although autonomic instability and mild pyrexia persisted. Thereafter she was maintained on oral diazepam (5mg six-hourly). Within 7 days she was asymptomatic and CPK and WCC had returned to normal levels. There was no evidence to support either a schizophreniform or an affective disorder prior to or during the illness or at the time of discharge. She was discharged home after 7 days on diazepam (5mg three times daily). It was noted in hospital records that during the past 10 years she had had three undiagnosed episodes of mutism and unresponsiveness during each of which she had been admitted to hospital and treated with antidepressants.

Episode Two

The patient was readmitted to the emergency unit 27 days later with a two-day history of mutism and immobility. On examination she was pyrexial, temperature 37,5 C, pulse rate 130/min., B.P. 150/100, respiratory rate 30/minute, and she was sweating. There was no dehydration and no muscular rigidity. On investigation, CPK was raised to 450 IU/L and she had a raised white cell count of 22,000 x 10 /L. Toxicology screen, CSR, lumbar puncture were normal. The only medication she had used was the prescribed diazepam (5mg three times daily) which she had discontinued a week following her previous discharge. She had not taken any neuroleptics nor other psychotropic agent, except diazepam.

A diagnosis of catatonia was made. The stuporous and immobile state altered to acute agitation after 24 hours, at which time she was inadvertently given haloperidol 10mg. i.v. for sedation. Within six hours she became profoundly stuporous once more, with marked diaphoresis, temperature 38,5°C, tachypnoea, and a persistent tachycardia of 150-160/min. Two additional features appeared, namely, muscular rigidity and an extremely elevated CPK (11,540 IU/L). The administration of diazepam (20mg i.v.) resulted in an immediate and dramatic resolution of the stupor and muscular rigidity. The patient was maintained on diazepam (20mg orally six-hourly) and remained mobile, alert and co-operative.

The autonomic instability persisted but gradually resolved over several days during which period the CPK and WCC returned

to normal levels. The patient was discharged home recovered, 7 days after admission, on diazepam (5mg. three times a day).

An appointment was given for follow-up.

Episode 3

The patient was readmitted to hospital a year later with a history of the acute onset of a mute and unresponsive state. She had defaulted from follow-up and had not taken diazepam or any other medication for approximately six months.

On examination she was mildly pyrexial, temperature 37,5°C, pulse rate 120/minute, respiratory rate 30/minute. Intermittent diaphoresis was noted. There was no muscular rigidity. She was negativistic, mute and posturing.

On investigation she had a raised CPK (395 IU/L), a normal WCC (8,5x10 /L) and low serum Iron [Iron 6 UMOL/L (normal 8-30); TIBC 65 UMOL/L (normal 48-67); % saturation 11% (normal 18-52)]. [An additional investigation of serum iron was carried out in view of a recent study (Rosebush & Mazurek, 1991) who noted frequent occurrence of a low serum iron concentration with the NMS.]

The patient's catatonic state responded well to diazepam intravenously, and thereafter she was maintained on oral diazepam and supportive care as in previous episodes. The autonomic dysfunction settled and CPK and Iron studies returned to normal levels within seven days.

SUMMARY OF CASE REPORTS

The six patients described presented to a local teaching hospital with an illness of acute onset, characterized by a mute and immobile state alternating with psychomotor agitation. There were four females and two males, with ages ranging between 20 years and 46 years. Five patients had no previous psychiatric history.

Following neuroleptic exposure all of them developed the clinical features characteristic of the neuroleptic malignant syndrome, namely an altered state of consciousness, muscular rigidity, pyrexia, autonomic instability, diaphoresis, as well as the laboratory findings of elevated CPK levels and leukocytosis (in 4 patients) which are commonly associated with the syndrome.

Iron studies undertaken in patient 6 showed a low serum iron concentration.

Four of the patients had no evidence of concurrent illness prior to the onset or during the NMS; one had radiographic evidence of patchy consolidation in the left lung and another had non-insulin dependent diabetes mellitus. Two had evidence of mild dehydration.

All patients were extensively investigated for a medical illness. Investigations included chest x-ray, VDRL, urinalysis, toxicology screen, blood culture, lumbar puncture,

EEG, C-T scan, serum biochemistry, full blood count, collagen screen.

Five patients had had no previous exposure to a neuroleptic nor any other form of psychotropic medication before admission to hospital. Patient 6 had been taking chlorpromazine 25mg. daily for a period of one month before admission.

All patients manifested the features of catatonia prior to neuroleptic administration.

The diagnosis of catatonia was based on DSM-III-R criteria for catatonia. The clinical features were consistent with catatonic mutism and catatonic excitement, every case displaying alternating episodes of mutism/stupor and excitement.

The neuroleptics administered included chlorpromazine, clothiapine and haloperidol.

Features of NMS emerged within 30 to 72 hours following administration of a single dose of a neuroleptic agent in patients 1 to 5.

All patients were managed with medically supportive measures during the acute illness. Various treatments were administered randomly during the acute phase as follows: Benzodiazepines had dramatic but short-lived effect in patient 1 and patient 6. Bromocriptine was prescribed for patient 4 with no effect. ECT x 2 administered to patient 1 during the acute phase of illness appeared to prevent deterioration. ECT administered

to patients 3 and 4 during the recovery phase was of doubtful benefit.

All patients had an uncomplicated course with no life-threatening sequelae. Duration of acute illness ranged from 5 to 14 days. Residual features of parkinsonism and mild fluctuations of pulse and blood pressure persisted for up to 28 days in some cases.

Following recovery two patients (5 and 6) had no evidence of psychiatric disorder. Two patients (3 and 4) had features of an affective disorder. Two patients had an atypical psychosis (1 and 2). Patients 1, 2, 3 and 4 were referred to another institution for management of the residual psychiatric disorder. Since patients 5 and 6 showed no residual psychopathology after NMS they were discharged home.

Following the acute illness, patients 1, 2 and 3 were challenged with clozapine for psychotic disorders between days 14 and 20 (with no ill effect). Patients 5 and 6 were discharged on small doses of diazepam. Patient 4 was treated with amitriptyline and ECT following the acute phase of NMS.

Two of the patients (3 and 6) showed intensified features of the NMS when neuroleptics were reintroduced during the acute phase of the illness. Patients 1 to 5 have remained well at follow-up and none is taking psychotropic medication. Patient 6 had a further relapse of catatonia (unassociated with neuroleptics) one year after discharge.

CHAPTER THREE

DISCUSSION

INTRODUCTION

The pathogenesis of the neuroleptic malignant syndrome and the predisposing/risk factors for the development of the syndrome are unclear. Numerous case reports and several retrospective analyses of chart data in the past decade have not only popularized the syndrome, but have also confused the clinician with disparate views concerning definition, aetiology, prevalence, pathogenesis and management of the disorder. Recent prospective studies (Addonizio, 1986; Deng et al. 1990; Rosebush & Stewart, 1989) have contributed more useful and consistent findings concerning the syndrome.

The outstanding feature in this group of patients was the catatonic state of acute onset (prior to neuroleptic exposure) which appeared to herald the emergence of the neuroleptic malignant syndrome.

Controversy exists concerning the relationship of NMS to catatonia. Some writers have attempted to define the syndromes as separate pathological entities (Castillo, 1988; Fleishhacker, 1989), whereas others have claimed that the similar clinical features suggest a common pathophysiology (Kellam, 1987; Mann et al. 1986; Price & Turnbull, 1989). The finding of an acute catatonic state in these patients,

prior to neuroleptic administration, supports the latter hypothesis. It is suggested that attempts to distinguish between the syndromes may be erroneous and mislead clinicians working in this field.

CLINICAL PRESENTATION

Patients 1 to 5 and patient 6 (episodes 2 and 3) presented with an initial illness of acute onset which was characterized by mutism, immobility, posturing, waxy flexibility, and negativism. This state alternated with episodes of acute psychomotor agitation and incoherence.

Following the meticulous piecing together of the examination and investigatory findings, with the preadmission information from family members and previous hospital data, the cluster of catatonic features emerged as the consistent and common finding in all patients "prior" to neuroleptic administration.

This observation has not previously been reported. Other investigators have noted that catatonia forms part of the symptom complex of NMS, usually reported as "following" exposure to neuroleptics (Addonizio, 1980; Fricchione, 1987; Rosebush, 1989).

Every patient in this group presented with episodes of "catatonic mutism", followed by psychomotor agitation which was attributed to a phase of "catatonic excitement". During the episode of excitement [psychomotor agitation], a

neuroleptic was administered in order to control behaviour; thereafter the patients developed a profoundly mute and stuporous state with autonomic instability, diaphoresis, pyrexia and extrapyramidal signs such as muscular rigidity in every case, and movement disorders of the extremities in some cases. These features are characteristic of the disorder that has been termed the neuroleptic malignant syndrome.

It is possible that the psychomotor agitation noted by others (Harsch, 1987; Itoh et al. 1977; Keck et al. 1989; Rosebush & Stewart, 1989) may have been part of a catatonic syndrome in the observed patients. It is suggested, therefore, that certain patients are admitted to hospital in a state of catatonic excitement (psychomotor agitation), are given neuroleptics to contain their behaviour and go on to develop an intensified catatonic state, with the additional feature of neuroleptic induced muscular rigidity, which is then diagnosed as the NMS.

This was exemplified by patient 6, in that her initial catatonic presentation, which included muscular rigidity, was associated with neuroleptic exposure prior to admission to hospital and therefore a diagnosis of NMS was favoured. However, the clinical features of the second catatonic episode were also indistinguishable from those of the first episode, except for muscular rigidity which was notably absent. During the second episode, muscular rigidity only appeared following the administration of a single dose of haloperidol, which was inadvertently given to control psychomotor agitation. In

addition, the features of catatonia in this episode were intensified following exposure to haloperidol, namely, autonomic instability and stupor. CPKmm levels also rose dramatically.

In reviewing individual reports in the literature, many of the cases described may have had a catatonic syndrome prior to the diagnosis of NMS:

Kish et al. (1990); Cases 1 and 5

Levenson et al. (1990); Cases 1 and

Levenson, 1985; Case 1

Castillo, 1989; Cases 1 and 2

Das Gupta (1991); Case Report

Singh et al. 1989; Case Report

Thacker et al. (1990) : Case Report

Kemperman, 1989: Case Report

Otani et al. (1991) ; Case Reports

Goldwasser et al. 1989 : Case Reports

Chayasirisabhon et al. 1983 : Case Report

Hermesh et al. 1987 : Case Report

Shalev et al. (1988) : Case Report

Goeke et al. (1991) : Case Report

LABORATORY FINDINGS

Traditionally the diagnosis of NMS has been made on clinical grounds and the non-specific laboratory findings of raised serum creatine phosphokinase (CPK) and leukocytosis being of supportive value in confirming the diagnosis. Recently Rosebush and Mazurek (1991), noted that a low serum iron concentration might also be associated with the syndrome.

CPK

CPK is found in muscle and brain tissue and provides a measure of tissue catabolism. There are three isoenzymes of which CPKmm most closely reflects muscle activity and integrity. CPKmm may be raised by skeletal muscle damage (as found in intramuscular injections, exercise, trauma and massage) and by some drugs, including succinylcholine alcohol and lithium. It is also raised in malignant hyperthermia, coma, infections, diseases involving muscle, convulsions, hyperthyroidism and possibly muscular rigidity.

In severe cases of NMS, rhabdomyolysis may cause myoglobinuria, and result in renal failure. In such cases CPKmm is drastically elevated with levels exceeding 30,000 I.U./L (normal level 50-110 I.U./L). The patients' described in this study showed moderately raised levels of CPK mm (range 622 to 1150 I.U./L). None of the patients had received an

intramuscular injection and there was no evidence of myoglobinuria. However, all six patients had muscular rigidity and therefore it would be logical to assume that elevated CPKmm in these cases was due to this rigid state. However, it is pertinent to note that patient 6 had a raised CPKmm level during the second catatonic episode prior to neuroleptic exposure and there was no clinical evidence of muscular rigidity. Following a single dose of haloperidol, the CPKmm rose dramatically and muscular rigidity appeared for the first time. The raised CPKmm, in the absence of rigidity in this instance, and the presence of persistent rigidity with normal CPKmm levels in patients 1, 2, 3 and 4 in the recovery phase indicate that CPKmm cannot be reliably attributed to rigid musculature.

It is suggested that an elevated CPKmm is not related to muscle rigidity but is indicative of the underlying catabolic process which is part of the catatonic syndrome preceding the NMS. It would appear that neuroleptics do not precipitate this process but in some cases, intensify the catabolic state of the antecedent catatonic syndrome as was demonstrated by patient 6 (episode two).

Our cases demonstrated that CPKmm levels were not an indicator of severity of illness as all patients were profoundly ill with marked stupor, autonomic dysfunction and muscular rigidity and yet the CPKmm level was only moderately raised (622 to 1185 I.U./L), and there was no evidence of myoglobinuria.

However, the CPKmm level was useful in confirming the diagnosis and in monitoring the acute phase of the illness: a rising CPKmm indicated an ongoing pathophysiological process whereas a falling CPK signalled the onset of recovery as became evident in the associated improvement of their clinical status. It is important to note that following the acute phase of NMS, some of our patients (1, 2, 3 and 4) remained markedly parkinsonistic with muscular rigidity for a period of days to weeks, with normal CPKmm levels.

Levenson (1985), included an elevated CPKmm as one of the three major criteria of diagnostic importance in NMS and inferred that a raised CPKmm differentiates NMS from catatonia. This study suggests that a raised CPKmm does not differentiate NMS from catatonia, but instead highlights the similarity between the two syndromes.

Serum Iron

Rosebush and Mazurek (1991), recently reported that out of 26 episodes of NMS, in 25 (96%) there was a dramatic fall in serum iron concentration in patients during the acute phase of the illness; this returned to normal in the recovery phase. Unfortunately, this investigation was not done in five patients in this study, but in view of the above report, serum iron studies were carried out during the third catatonic episode in patient 6. A low serum iron concentration was observed during this episode of catatonia (unassociated with

neuroleptics), which returned to normal during the recovery phase.

Hypoferraemia is known to occur in febrile conditions, strenuous exercise, and in myocardial infarction as part of an acute phase reaction (APR). Rosebush and Mazurek (1991), have postulated that NMS may be an acute phase reaction (APR). This is a complex physiological response, which sets off a wide range of events including fever, leukocytosis, muscle breakdown and hypoferraemia: these are all characteristic of the NMS. They stated that the mechanism by which the APR might be initiated in NMS is unclear. The finding of a low serum iron concentration in our catatonic patient (unassociated with neuroleptics) suggests that the APR may be a physiological disturbance associated with a catatonic state. It is probably incorrect, therefore, to assume that the APR is a pathognomonic feature of NMS. If this response is common to both catatonia and NMS, it highlights the similar pathophysiology of the two disorders.

PATHOPHYSIOLOGY

The Role of Dopamine

There is evidence that NMS may be related to a central dopamine deficiency predominantly in the nigrostriatal and mesolimbic pathways. Altered dopaminergic activity in the anterior hypothalamus may account for the autonomic dysfunction and hyperthermia (Horn et al. 1988; Fricchione, 1985; Mueller, 1983).

Reduced dopaminergic transmission in the diencephalon has also been postulated to explain the hyperthermia and catatonic signs described in lethal catatonia (Christoffels, 1970; Kick, 1981; Powers et al. 1976; Tolsma, 1967).

If a hypodopaminergic state exists in catatonic patients, it would be logical to assume that this deficiency would be aggravated by the dopamine blockade imposed by neuroleptics. This hypodopaminergic crisis in certain neurotransmitter pathways then manifests with the clinical features recognized as the NMS.

The role of Serum Iron

Recently, considerable attention has been given to the role of serum iron and the maintenance of normal dopaminergic function in the brain. Iron is present in relatively large quantities in the brain and its distribution roughly parallels that of dopamine with highest concentrations in basal ganglia (Ben-Shacher, 1985). There is evidence that iron may be integral to normal function of the dopamine (D2) receptor. Rats made iron deficient have a reduced response to the dopamine mediated behavioural and physiological effects of apomorphine and have fewer D2 receptors without any apparent change in D1 receptors.

Clinical studies have further demonstrated the association between serum iron and D2 receptor function. The "restless legs" syndrome is associated with iron deficiency anaemia.

This syndrome has been identified as virtually identical to neuroleptic induced akathisia, which is thought to be related to D2 receptor blockade (Editorial: Lancet, 1986).

Rosebush and Mazurek (1991), suggested therefore that a decrease in serum iron may lead to a decrease in D2 receptors in the brain. In the presence of further dopamine blockade by neuroleptics, this further loss of receptors may trigger an acute reduction of dopaminergic function, thereby potentially contributing to the clinical features characteristic of the NMS. They contended that serum iron may be a useful biological marker for the NMS and a helpful adjunct in the diagnosis of the disorder.

The additional finding of a low serum iron concentration in the third catatonic episode in patient 6 (unrelated to neuroleptics) is therefore highly pertinent and highlights again the similar pathophysiology between NMS and catatonia.

This finding casts doubt on the usefulness of a low serum iron as a useful biochemical marker for NMS as suggested by Rosebush and Mazurek (1991). A low serum iron concentration may be a feature of catatonic states in general rather than the NMS per se.

Malignant Hyperthermia (MH) and the Neuroleptic Malignant Syndrome (NMS)

Controversy exists concerning a possible pathophysiological relationship between NMS and MH.

Both syndromes are characterized by fever and delirium, a hypermetabolic state of skeletal muscle and rhabdomyolysis. The possibility of an aetiological connection has been strengthened by reports of abnormal contractile response of skeletal muscle in vitro to halothane exposure in patients who developed NMS. Although theories of a neurogenic origin were proposed, evidence indicates that malignant hyperthermia is a disorder affecting skeletal muscle in which the concentration of calcium in the myoplasm rises uncontrollably during exposure to triggering drugs such as halothane and succinylcholine. The NMS is postulated to be a disorder of central neurogenic origin precipitated by the dopamine blocking activity of neuroleptics on dopaminergic neurotransmitter pathways in the brain.

Due to the skeletal muscle response to halothane in 5 of 7 cases of NMS, Caroff et al. (1987), postulated that the development of rigidity in NMS is a function of a similar skeletal muscle abnormality as in malignant hyperthermia patients, triggered by neuroleptics. None of the NMS/MH or control group in the study showed a significant difference in response to fluphenazine. This finding suggests that although NMS patients may be MH susceptible, the converse does not apply.

Tollefson, (1982), Scarlett (1983) and Merry et al. (1986), reported contrasting evidence for MH susceptibility in NMS, in observing that the tissue from NMS patients did not respond abnormally to halothane, caffeine or other agents. Clinical evidence indicates that NMS patients tolerate anaesthetic agents without incident (Levenson et al. 1987, 1988; Lostra et al. 1983). Adityanjee (1988), described a case of NMS in a young girl who was given ECT x 6 under general anaesthesia with exposure to succinylcholine with no adverse effect.

Goeke et al. (1991), administered ECT x 13 under general anaesthesia to a 42-year old female following NMS. In every anaesthetic the patient was given intravenous methohexital, succinylcholine and labetolol. The CPKmm, serum potassium and temperature were monitored during each ECT and remained stable.

Three of our patients were given ECT under general anaesthesia in the recovery phase of NMS, which totalled seven exposures to thiopentone and succinylcholine and there were no adverse effects. Specifically there was no evidence of fever, rigidity or elevated CPKmm during or following the anaesthetic exposure.

We have provided clinical and laboratory evidence which suggested that NMS and catatonia share a common pathophysiology. Based on clinical and laboratory similarities, Caroff et al. (1987), have postulated a pathophysiological link between NMS and MH. If NMS is a neuroleptic intensified form of catatonia as we have

postulated, then according to Caroff's hypothesis it would be logical to assume that catatonic patients may be MH susceptible. It is interesting to note, however, that ECT under general anaesthesia has historically been the treatment of choice for catatonia, but to date there have been no adverse consequences reported, specifically any occurrence of MH, following exposure of catatonic patients to anaesthetic agents. Likewise, not a single case of MH has been reported in the literature in NMS patients exposed to MH triggering agents.

Despite the persuasive clinical data, anaesthetists continue to view NMS with a high index of suspicion and avoid the use of triggering agents such as succinylcholine in known NMS patients.

Further clinical and laboratory studies may help to clarify this issue.

PREDISPOSING FACTORS

Catatonia

Several authors have commented that affective disorder is a common antecedent diagnosis in patients who develop NMS, and that patients with schizophrenia have the lowest incidence of NMS (Addonizio et al. 1986; Keck et al. 1987; Levenson et al. 1988; Rosebush & Stewart, 1989).

The finding of a low incidence of NMS in patients with schizophrenia may be explained by the hyperdopaminergic state postulated as the underlying neurochemical imbalance in schizophrenia which may be a protective factor against the deleterious effects of neuroleptic induced dopamine blockade. Furthermore, studies have shown an infrequent association between catatonia and schizophrenia.

Initially, the patients with catatonia in this study were not assigned to another diagnostic category since none had a known previous psychiatric history. Following the acute illness, two patients were eventually diagnosed as having an affective disorder, two had an atypical psychosis and two patients had no residual psychopathology: there were no patients with schizophrenia.

These findings are in accordance with those of other investigators (Abrams et al. 1976; Barnes et al. 1986; Kish et al. 1990; Mann et al. 1986), who have suggested that catatonia appears to be an acute neuropsychiatric syndrome of limited duration, which may arise during the course of an affective disorder, organic disorder or from an undetermined aetiology. Catatonia is classified under the schizophrenic disorders in DSM III-R and ICD 9. Due to this historical classification, a diagnosis of catatonia has been universally considered to be synonymous with that of schizophrenia. This is unfortunate since patients such as those described above, who present with catatonia, are at risk for being diagnosed as

having schizophrenia, which is not only erroneous, but may serve to stigmatize the patient.

Psychotropic medication and NMS

All neuroleptics, including the newer generation drugs such as clozapine, have been documented as causal agents in the development of the NMS (see literature review). Keck et al. (1989), have suggested that the rate of neuroleptic dose increase and maximum neuroleptic dose administered may represent significant risk factors for the development of the syndrome. Rosebush (1989), suggested that the introduction of neuroleptics for the first time, or a dosage increase in a person, who is vulnerable, may account for the development of the NMS.

Our patients had no previous exposure to neuroleptics and received only one or two doses of medication. The neuroleptics administered to these patients included clothiapine, chlorpromazine and haloperidol. The findings support those of Rosebush (1989), as the emergence of NMS in all patients appeared to follow the initial introduction of neuroleptics. In view of these findings, it is probable that the vulnerable state referred to by Rosebush is the antecedent

catatonic state which predisposes such patients to the deleterious effects of even a single dose of neuroleptic agent.

Genetic factors

Otani et al. (1991), postulated that NMS may be genetically transmitted. They described the findings in a Japanese family where the mother and two daughters were noted to have had separate episodes of catatonia (not associated with neuroleptics), severe neuroleptic induced extrapyramidal symptoms and episodes of NMS. They concluded that the predisposition to NMS may be trait dependent.

Patient 6, in this series demonstrated similar features with episodes of catatonia which were diagnosed as NMS only when associated with neuroleptics and the presence of muscular rigidity. If NMS is a catatonic state intensified by neuroleptic administration as suggested previously, then certain patients may have a trait dependent predisposition to catatonia, which manifests as NMS following neuroleptic exposure.

CNS Disorders

Several authors have commented on the association of the NMS with underlying brain disorders, other than psychiatric disorders. Fricchione (1985), and Rosebush (1989), suggested

that CNS compromise may increase the risk of developing NMS. The CNS disorders include mental retardation, Alzheimer's disease, Cerebral vascular accident, Post-traumatic brain syndromes, seizure disorders and AIDS. None of these patients were found to have any associated CNS pathology prior to the onset of illness.

Differential Diagnosis

Patients who present with the cluster of clinical features suggestive of NMS require thorough investigation to exclude other causes of pyrexial and stuporous states.

To exclude drug toxicity, dehydration and infections, all patients were screened by investigations which included toxicology screen, urinalysis, mid-stream urine; chest radiography, V.D.R.L., full blood count, cerebro-spinal fluid, Electroencephalogram, C-T scans, and serum biochemistry.

Patient 1 had radiographic evidence of patchy consolidation in the left lung. Consequently a pneumonic process with septicaemia was considered to be a contributing factor to the physical state. However, this finding could not account for stupor and neurological abnormalities of muscular rigidity and tremor: the pneumonia was probably a sequel to the initial illness.

Patient 4 had late onset diabetes mellitus and essential hypertension. A diagnosis of a cerebral vascular accident

(C.V.A.) was considered to be a possible cause of aphasia. As other signs appeared, such as tachycardia, labile blood pressure and sweating, an alternative diagnosis of an acute alcohol withdrawal state with delirium was considered. Certain features of NMS resemble the alcohol withdrawal syndrome with delirium (autonomic arousal, sweating, tremor, incoherence), but this diagnosis is not usually accompanied by stupor, extrapyramidal signs and raised CPK levels, which emerged in this patient.

The patient's diabetes and blood pressure were well controlled, and investigation ruled out C.V.A. as a cause of mutism. A blood count and liver profile provided no evidence for alcoholism.

Central Nervous System Infection was considered as a possible cause of illness in every case. Lumbar puncture, V.D.R.L., E.E.G. and C-T scan were carried out and proved to be non-contributory. Case 5 was investigated for neurosyphilis due to the F.T.A. and an abnormal E.E.G., but the CSF was normal and the non-specific E.E.G. findings were attributed to a metabolic encephalopathy accompanying the catatonic state.

Dehydration has been cited as a possible predisposing factor for the NMS. Rosebush and Stewart (1989) found dehydration present in 96% of their cases. Two of our group presented with mild dehydration which preceded the onset of NMS. It is difficult to determine if this factor contributed to the severity of the illness. The patients who were not dehydrated had as severe an illness as the two presenting with

dehydration. The correction of fluid and electrolyte balance in these cases was not associated with clinical improvement. It appears that dehydration does not have a role in the pathophysiology of the disorder, but is an associated feature which may complicate the course of the illness.

MANAGEMENT OF THE NEUROLEPTIC MALIGNANT SYNDROME

All patients recovered and did not develop medical complications during the course of illness, apart from the single instance of pneumonia. The uneventful outcome can be attributed to early recognition of the disorder and timely intervention along the following lines:

General Measures in Treatment of NMS

- * Once the diagnosis is suspected, it is recommended that all patients be admitted to a medical ward for the management of the acute phase of the illness.
- * Fluid and electrolyte balance requires urgent correction and thereafter intravenous maintenance. Nutrition is maintained via nasogastric feeding during the stuporous and immobile phase of illness.
- * Neuroleptics must be immediately discontinued.

- * Urinary catheterisation during the acute phase of illness permits the monitoring of urinary output and the recognition of abnormal constituents such as myoglobin.
- * Daily serum samples are taken for the measurement of electrolytes, urea, creatinine, serum iron, CPK and white cell count.
- * The rigid and immobile physical state predisposes the patient to complications such as aspiration and hypostatic pneumonia, and deep vein thrombosis. Physiotherapy is therefore an important adjunct in the prevention of these potentially life-threatening complications.
- * Once the diagnosis of NMS has been established, it is useful to monitor progress by recording daily clinical and investigatory data on a flow sheet.

These patients were managed by a combined multidisciplinary team consisting of a physician, a psychiatrist, psychopharmacologist, trained nurses and a physiotherapist.

Pharmacotherapy

As previously mentioned, pharmacotherapy is of limited or doubtful value in the treatment of the NMS. Specifically, there is inconsistency about the efficacy of drugs such as bromocriptine and dantrolene. In an overview, Fricchione (1985), advocated the use of benzodiazepines due to the

dramatic, although short-lived, response noted in some cases of NMS. Rosebush and Stewart (1989), recommended using benzodiazepines as part of treatment to relieve the patient's discomfort and to decrease the hyperadrenergic state which, they claimed, may contribute to the pathophysiology of the disorder.

Benzodiazepines

In the management of our group of patients, supportive care was the mainstay of treatment, but diazepam was prescribed where necessary for those patients who were restless and required sedation. Patient one showed a dramatic but temporary improvement in mental state following an intravenous dose of this agent which was given for diagnostic purposes.

Patient 6 had a similar response to intravenous diazepam in every catatonic episode. Following the initial intravenous dose, a daily oral regime was prescribed, which maintained the improvement in mental status. Diazepam also improved muscular rigidity, but other features such as autonomic instability, pyrexia and raised muscle enzymes persisted and eventually resolved independently of the diazepam administration.

We found that benzodiazepines played a valuable role in the responsive patient in early mobilisation and autonomy in the areas of promoting feeding and self-care, thereby preventing possible life threatening sequelae.

I share the view of Menza and Harris (1989), who commented, in an overview of the role of benzodiazepines in catatonic states, that agents such as diazepam and lorazepam have a role in the evaluation and management of the catatonic patient.

It is important to emphasize, however, that the benzodiazepines do not appear to have an effect on the core metabolic dysfunction of the disorder.

Bromocriptine

Bromocriptine was prescribed for patient 4 (10mg. t.i.d.) over a period of three days with no apparent beneficial effect, and was therefore discontinued. (Being a dopamine agonist, this agent may have the adverse effect of inducing or worsening psychotic illness.)

Dantrolene Sodium

Dantrolene [used intravenously in doses of 50mg. 12 hourly, up to 7 doses], a skeletal muscle relaxant, was not prescribed for any of our patients. (Apart from inconsistent reports of efficacy in NMS, this drug has the potential problem of causing hepatic toxicity.)

ECT

ECT should be used cautiously and not as the treatment of choice during the acute phase of illness. However, where there is a deterioration in the clinical state of the patient following supportive treatment as demonstrated in patient 1, ECT may be considered.

The evidence concerning the safety and efficacy of this procedure remains largely anecdotal and requires further investigation.

TREATMENT OF THE UNDERLYING PSYCHIATRIC DISORDER FOLLOWING RECOVERY FROM NMS

Challenge with Neuroleptics

Evidence has accumulated which suggests that certain patients resume neuroleptic therapy successfully with no sign of recurrence of NMS (Levenson & Fisher, 1988; Pope et al. (1990). Of particular note are the findings of Rosebush and Stewart (1989), who successfully challenged 13 (87%) of their 15 patients. Five of the fifteen patients had a recurrence of symptoms when challenged initially. Four of these were re-challenged with symptoms developing in two cases, finally one of these was successfully challenged a third time without recurrence of symptoms. Analysis showed that a period of over two weeks before re-challenge was significantly associated

with success. Their study showed that a lower drug potency and dosage at challenge were not statistically significantly related.

The observations made in this study of 6 patients are in accordance with the above findings. In some cases the challenge was accidental, e.g. patient 3 was inadvertently challenged with haloperidol on day 9 to control agitation during the acute illness which caused an exacerbation of symptoms. However, there was no sign of a recurrence when deliberately re-challenged with clozapine on day 18 during the recovery phase.

Patient 6 was also inadvertently given a doze of haloperidol during the second catatonic episode, which caused an intensified catatonic state. CPKmm levels rose dramatically and muscular rigidity appeared with the result that the clinical picture in this episode was indistinguishable from the NMS.

Patient 1 accidentally received a single doze of clothiapine on day 14, during recovery which caused marked extrapyramidal signs, but CPKmm levels remained normal and no further signs of NMS developed later. She was challenged with clozapine on day 17 to treat psychotic symptoms, with no signs of recurrence.

Patient 2 was challenged during recovery with clozapine on hospital day 6 and showed no signs of recurrence.

In summary, therefore, two patients (3 and 6) showed an intensification of symptoms when neuroleptics were given inadvertently in the acute phase of illness. However, three patients (1, 2, 3) re-challenged with neuroleptics in the recovery phase, showed no signs of recurrence of NMS.

Despite the limited experience gained in this study, it would appear that neuroleptics may be used to treat post-NMS psychosis provided they are reintroduced following the resolution of the antecedent catatonic state. It is suggested that neuroleptics should not be considered until there is a marked improvement in clinical status and the CPKmm, serum iron and white cell count are within normal limits.

Neuroleptics Contraindicated in the treatment of Catatonia

The profound illness in this group of patients appeared to be precipitated by neuroleptic administration, which indicates the potential hazard of using these agents to treat catatonia.

Certain writers continue to emphasize the differences between catatonia and NMS for the purpose of treatment (Fleishhacker et al. (1991)). While it has been accepted that the immediate cessation of neuroleptics is imperative in the treatment of NMS, neuroleptics are recommended as the treatment of catatonia. It is unfortunate that this approach has been reinforced by the literature.

For example, Rosebush and Stewart (1989), in their discussion of NMS, stated that "patients with so-called psychogenic catatonia usually improve rather than worsen when given neuroleptics".

Goeke et al. (1991), in their description of a case of lethal catatonia complicated by NMS following neuroleptic administration, commented "the management of lethal catatonia requires the use of antipsychotics or neuroleptic medication, while the cornerstone of NMS management is the discontinuation of such medication".

This study highlights the fact that the use of neuroleptics is a dangerous procedure in catatonic patients and is contraindicated in the treatment of this disorder.

OUTCOME

The natural course of the syndrome is towards recovery with supportive care and the discontinuation of neuroleptics. A fulminating course with fatal outcome is usually associated with failure of recognition of the syndrome and continued administration of neuroleptics. This was illustrated by three cases of fatal hyperthermia described by Kish et al. (1990), where neuroleptics were not discontinued despite the presence of the diagnostic features of NMS. Mann et al. (1986), commented in a review of 292 cases of lethal catatonia, that

65 (22.3%) fatal episodes were associated with neuroleptic exposure.

The long term outcome regarding a recurrence of NMS in these patients is unknown as none of them needed on-going neuroleptic therapy, and at the time of writing all patients were well at two to four years follow-up. It is interesting to note that Pope et al. (1991), in their study of 22 patients who had experienced episodes of NMS, found that 11 of the 20 who resumed neuroleptics after the index episode have had no recurrences of the syndrome after collectively receiving 16 years of neuroleptic exposure.

If NMS is an intensified form of catatonia, as hypothesized, it is highly probable that should any of the patients develop another catatonic episode, features identifiable as the NMS would develop following neuroleptic exposure.

FUTURE RESEARCH

During the present decade there has been an increasing awareness and recognition of the entity termed the neuroleptic malignant syndrome. Recent studies have provided more consistent data and possible risk factors have been suggested which may predispose a patient to the NMS.

It has been hypothesized from the findings in this small study that NMS and catatonia probably share a common pathophysiology and that certain cases of the NMS are probably an intensified

form of the catatonic state that preceded neuroleptic exposure.

This hypothesis needs investigation at both the clinical and laboratory level to clarify the correct nosological status of catatonia and NMS.

A further area to investigate is the occurrence of biochemical findings such as abnormal levels of CPKmm and serum iron in other psychiatric disorders in order to determine if these abnormalities are specific to catatonic states.

As regards management, the efficacy of pharmacotherapy and ECT in the acute and recovery phase of NMS/catatonia needs further evaluation.

The controversy about MH susceptibility in NMS patients which has led to the avoidance of the use of succinylcholine when administering a general anaesthetic to NMS patients, needs to be resolved by systematic clinical and laboratory study. In a laboratory setting this may require the inclusion of a group of non-NMS but neuroleptic exposed psychiatric patients, in addition to the three groups already studied (NMS patients, MH patients, and normal controls).

Unfortunately, the paucity of patients presenting with features of NMS pose problems for future research. Deng et al. (1990), commented that "the conundrums of neuroleptic malignant syndrome will remain unresolved until a uniform protocol for case ascertainment, data collection and treatment is prospectively applied at a large number of psychiatric

centres". They advocated the need for a multicentre collaborative study.

CONCLUSION

The neuroleptic malignant syndrome has been discussed from the perspective of the findings in a small group of patients. The outstanding feature in all of these cases was a catatonic state of acute onset which preceded neuroleptic administration and the emergence of the so-called neuroleptic malignant syndrome.

The similar clinical and laboratory features of NMS and catatonia noted in these patients reflect the probable common pathophysiology and unitary nature of the disorders.

Comments in recent literature, "where have all the catatonics gone?" (Mahendra, 1981) and "while the use of antipsychotic agents has nearly eradicated lethal catatonia, it has led to the emergence of the NMS" (Goeke et al. 1991), draw attention not only to the disappearance of catatonia, and the probable over-reporting of NMS, but highlight the loss of perspective concerning these disorders.

In revising the nosology which presently embraces catatonia and NMS as separate disorders, it is necessary to liberate scientific reasoning from the restraints imposed by a seductive terminology.

It is suggested therefore that the term neuroleptic malignant syndrome is misleading and no longer serves a useful purpose. The broader category of catatonia is preferable as the primary diagnosis, which provides the clinician with a wide range of options when exploring possible contributory or aetiological factors bearing on the catatonic state.

ACKNOWLEDGEMENTS

I wish to express special thanks to Dr. Eleanor Nash for her interest and advice as supervisor of this dissertation.

Also thanks to Dr. Ashley Robins, without whose encouragement these findings may not have been recorded.

Grateful thanks to my typist, Pat Boulton, who had the arduous task of preparing this manuscript.

And finally, thank you to my family, who have been unreservedly supportive and understanding.

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