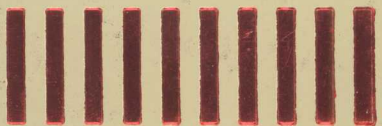
Neuroleptic Malignant Syndrome

A CLINICAL APPROACH



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To Linda and Bill,
and our children, David, Benjamin, Nicole, Julianne,
Margaret, Katherine
With love

Preface

Over the past 30 years the field of psychiatry has been revolutionized by the treatment of psychoses with neuroleptic medication. Patients who had been rendered totally disabled by their illness could now function and lead productive lives. In spite of this major advance, problems remain. Many patients suffer severe side effects, and others are resistant to the therapeutic effects of neuroleptics. Over the past 10 years clinicians from many disciplines have become increasingly aware of neuroleptic malignant syndrome (NMS), a potentially deadly side effect of neuroleptic treatment. Our own personal observations of this devastating illness as well as the growing number of reported cases drew our attention to this disorder. Increasing recognition of NMS has led to numerous case reports and reviews of the literature, but many questions remain to be answered. The literature is replete with conflicting views about every aspect of NMS, including how best to care for these patients. Although such controversy stimulates needed research, clinicians who search the literature for guidance will find widely divergent points of view.

It was just this clinical need that we attempted to fill in writing this book. Our aim was not to create answers where there are none, but to review what is known, present the controversies, then make recommendations based on a comprehensive and critical review of all of the data. In so doing we hope to help the clinician to intervene quickly in this potentially lethal disorder. We also hope that focusing on the controversies and on our lack of knowledge will help direct researchers toward critical areas of investigation. Our last wish is that we do not

dissuade physicians from the prudent use of neuroleptic medication by highlighting the dangers of NMS, but that by having a full understanding of this disorder clinicians will be allowed to utilize the extraordinary benefits of these medicines with the greatest measure of safety.

Gerard Addonizio, M.D.
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HISTORICAL PERSPECTIVE

In the midst of a rapidly expanding literature on neuroleptic malignant syndrome (NMS), it is worth noting that syndromes similar to NMS were frequently described in the psychiatric literature years before neuroleptics entered the armamentarium of medical practice. In 1832 Calmeil described patients who were agitated, psychotic, and stuporous and died with hyperthermia.[1] In 1849 Bell reported on a disorder he found in 40 of 1,700 patients admitted to the McLean Asylum over 12 years.[2] The patients were described as psychotic, agitated, febrile, delirious, tremulous, tachycardic, diaphoretic, and rigid. Most of these cases resulted in death without any clear identifiable cause on autopsy. Bell concluded that "the final result of all the attempts to bring its characteristics to the standard of any described form of disease is in my view, that it must be regarded as one of the nervous derangements which has hitherto been overlooked and undescribed." In 1934 Stauder coined the term *lethal catatonia* for the disorder.[3] This term has gained widespread use and is probably the one used most frequently by authors describing the syndrome.

In 1947 Adland published a detailed review of the literature on this syndrome, which he called the acute exhaustive psychoses.[4] He pointed out that the disorder had been described under various names: acute delirium, fatal catatonia, acute dementia praecox, manic-depressive ex-

haustive death, acute idiopathic psychosis, brain death in schizophrenia, Scheid's cyanotic syndrome, and Bell's mania. These cases often exhibited extremely high fevers and marked leukocytosis. Patients who developed the syndrome were frequently believed to be manic-depressive. Adland also said:

> Thus, the review of the literature indicates several main trends. There have been some investigators who consider this syndrome to be merely secondary to an infectious process. There were those who held that death in this primary syndrome is caused by increased intracranial pressure. Others considered the syndrome an idiopathic intoxication, causing definite cellular changes in brain, primarily lipoid changes. Some workers have postulated a toxic factor (possibly histamine or histamine-like) which disrupts the normal functioning of the hematopoietic and cardiovascular systems. The present author believes that this illness originates as a psychogenic problem and that the psychopathology—the dynamic of the disorder—is expressed through dysfunctions of the cardiovascular, heat regulatory and hematopoietic systems.

This controversy seems remarkably similar to some of the current debate concerning the nature and cause of NMS, as is discussed later in this chapter.

INITIAL RECOGNITION AND DEFINITION OF THE SYNDROME

With the advent of neuroleptic treatment in Europe in the 1950s it gradually became clear that numerous adverse effects were associated with the use of these agents. Most prominent was the appearance of extrapyramidal symptoms (EPS) such as rigidity, tremors, dystonia, akinesia, and akathisia. In the 1960s Delay and Deniker[5] began to recognize what they described as the "most serious," "rarest," and "least known" of the complications of neuroleptic therapy. They called this disorder neuroleptic malignant syndrome. These patients developed extremely high temperatures, severe EPS, stupor, and pulmonary complications. The outcome could be fatal. They believed that NMS occurred selectively in brain-damaged patients who received neuroleptic drugs. In their experience they remarked that they had seen five cases of NMS out of several hundred cases of neuroleptic treatment.[6] This observation became the basis for the expected incidence of NMS for the next 20 years until further recognition of the syndrome prompted more rigorous prospective and retrospective analyses with strict diagnostic criteria.

Except for an occasional case report, NMS was largely ignored in the English language literature. In 1973 Meltzer[7] reported on a schiz-

ophrenic patient who developed NMS after receiving fluphenazine enanthate. The patient developed rigidity, hyperthermia, tachycardia, hypertension, incontinence, tremors, and unresponsiveness. He lapsed into coma but ultimately survived. Meltzer pointed out that the patient's creatine phosphokinase (CPK) level increased during the episode. This was an important observation, as an elevated level of CPK has come to be a significant biologic marker in identifying and tracking the course of NMS. He also drew attention to a potential association between NMS, malignant hyperthermia, and lethal catatonia. Malignant hyperthermia, a pharmacogenetic disorder of muscle, results in severe rigidity and hyperthermia when susceptible patients are exposed to succinylcholine or inhalation anesthetics. The similarity in clinical manifestations of NMS and malignant hyperthermia led to numerous studies attempting to link NMS to muscle disease. Although no definitive conclusions have been reached, this research continues to be an intriguing area of study (see Chapters 6 and 7).

The relationship between NMS and lethal catatonia also continues to be of great interest, as both disorders can have an identical presentation. In 1973 Meltzer[7] wrote: "Whether or not there is a neuroleptic 'malignant' syndrome apart from 'acute lethal catatonia' will remain difficult to ascertain until the syndrome occurs in a non-psychotic patient taking phenothiazines." Over the next 15 years the literature[8–10] provided evidence that NMS occurred in nonpsychotic patients. Nevertheless, the relationship between NMS and lethal catatonia continues to be important, since clinically differentiating one from the other can be extremely difficult. Mann and colleagues[3] reviewed 292 cases of lethal catatonia and found that the clinical phenomenology was consistent with the diagnosis of NMS in 65 cases. They pointed out that lethal catatonia is a syndrome that can have various functional or organic causes and that NMS may just be one form of a more general syndrome.

Further attention was drawn toward NMS-like syndromes with the publication in 1974[11] of four cases of agitated manic patients who appeared to have a toxic reaction to the combined treatment of high doses of lithium and haloperidol. These patients developed lethargy, fever, EPS, confusion, and leukocytosis, thereby fulfilling criteria for NMS. Two patients had irreversible brain damage. The publication of these cases spread fear in the psychiatric community about the combined use of lithium and haloperidol despite evidence that the combination presents no special danger[12] (see Chapter 3). In 1977 Gelenberg and Mandel[13] called attention to the ability of high-potency neuroleptic drugs to cause catatonic reactions. They presented eight cases in which

features of catatonia and parkinsonism occurred while patients received treatment with high-potency neuroleptic drugs. They also pointed out that this syndrome could easily be confused with a worsened schizophrenic state. This view was echoed in 1978 by Weinberger and Wyatt[14] who stated, "that a therapeutic agent might cause a syndrome indistinguishable from the one which it serves as treatment is a clinical paradox rarely encountered in medical practice."

REFINEMENT OF THE CLINICAL DEFINITION AND CRITERIA

In 1980 Caroff[15] published a review of over 60 cases of NMS that existed in the world literature at that time. This was the first detailed review of the clinical characteristics and differential diagnosis of NMS in the English language literature. The report by Caroff was a turning point in the establishment of NMS as an important concern for those using neuroleptic medication. Wider recognition of the syndrome resulted in a rapid rise in the reporting of cases. Just 6 years later Pearlman's[16] review of NMS listed 320 reported cases in the literature. It is possible that increased recognition also affected mortality rates in cases reported in the literature, as mortality decreased from approximately 22% of cases through 1980 to 4% of the last 50 in Pearlman's review.[16] Some investigators[17] have believed that the upsurge in reported cases of NMS is the result of vague diagnostic criteria. However, when strict diagnostic criteria have been used in studies of NMS, frequency rates have ranged from .07%[18] to 2.4%[19] in patients treated with neuroleptic drugs. Levenson[20] developed criteria for the diagnosis of NMS utilizing a list of major manifestations (fever, rigidity, elevated level of CPK) and minor manifestations (tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, leukocytosis). If all three major manifestations were present or if two major and four minor manifestations were present, a high probability of NMS would be indicated when supported by clinical history. Although these criteria represented progress in defining NMS, they have been criticized on the basis that NMS should not be diagnosed in the absence of rigidity and that an increased level of CPK should not be a major manifestation.[21]

In addition to questions about sound diagnostic criteria, some investigators[22] criticized the diagnosis of NMS on the basis that many cases of purported NMS were actually cases of patients who developed rigidity secondary to receiving neuroleptic drugs and simultaneously developed fevers secondary to concomitant medical illnesses rather

than a neuroleptic-induced hypothalamic dysregulation. Others[23] argued that although this claim seemed justified in some cases, it did not hold true for the majority.

Other long-held notions about NMS came under scrutiny. For many years NMS was thought to be an idiosyncratic reaction that progressed rapidly in a fulminant way. Further examination by several investigators[19, 23] has questioned this and has suggested that although NMS occurs explosively in some patients, in others it occurs more gradually and with less severity, thereby indicating that NMS may be a spectrum disorder with a range of deleterious effects. Conflicting ideas about these conceptual models await further studies to establish their validity. Another long-held notion about NMS has been that it is largely a disorder of young adults,[15] and until recently the literature generally supported this idea. We now know that this is not true and that many elderly patients suffer the devastating effects of NMS.[24]

Investigation into the biologic basis of NMS has begun (see Chapter 7), but to date our knowledge has not progressed much further than what we know by extrapolating from the general effects of neuroleptic drugs on the central nervous system. Interesting treatments with agents such as bromocriptine and dantrolene have yielded dramatic results in some cases, but one prospective study[25] suggests that these treatments may confer no advantage over supportive care (see Chapter 10). Ideally, careful treatment studies of NMS will bring us beyond a suggested treatment of an NMS-like state in 1849,[2] which consisted of "wine, whey, toddy, and other diffusible stimulants."

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DEMOGRAPHICS AND RISK FACTORS

Although neuroleptic malignant syndrome (NMS) seems to be relatively uncommon and occurs in patients with different demographic profiles, it is valuable to attempt to identify predisposing risk factors. Identifying such factors is difficult because of the low incidence of the syndrome. Nevertheless, many large reviews and retrospective studies in addition to prospective surveys have provided a larger pool of data on which to base some preliminary conclusions. This chapter addresses the incidence of NMS and the risk factors for this disorder as they have emerged from the literature.

INCIDENCE

The incidence of NMS among male and female inpatients has been estimated to be between 0.07% and 1.4%.[1–6] An even higher incidence of 2.4% was identified in a retrospective study[7] designed to maximize the likelihood of discovering cases of NMS by restricting the study population to acutely psychotic young men. The incidence of 0.5% to 1.0% reported by Delay and colleagues[1] represented the only data on

incidence for over 20 years. In 1986 Pope and colleagues[2] reported the higher incidence of 1.4% in a retrospective review of 500 patients treated with neuroleptic drugs at McLean Hospital, a private facility. The same group[3] then did a prospective study and found the somewhat lower incidence of 0.9% among 679 patients. Two subsequent prospective studies found even lower incidences of 0.2% among 495 patients[4] and 0.07% among 1,470 patients.[5]

Most recently the McLean group completed a retrospective study at a state hospital and again found a 0.9% incidence among a population of 551 patients.[6] In that article they addressed possible explanations for the disparate rates reported to date and drew attention to the potential influences of varying patient populations, lengths of stay, and medication practices. They suggested that higher incidence rates may occur in facilities that treat more manic patients and in which patients stay longer, because the risk period for development of NMS is effectively increased by prolonging the time a patient receives neuroleptic drugs. They also hypothesized that some centers may practice more conservative dosage strategies or may be more aware of the potential for developing NMS, consequently reducing the chances for the full syndrome to occur by using smaller amounts of neuroleptic drugs and more quickly recognizing early manifestations of the syndrome and discontinuing treatment with such drugs.

Another major source of the discrepant incidence rates may be the ongoing debate about whether NMS is a spectrum disorder.[2, 3, 7–10] Full-blown NMS, with dangerously elevated temperature, profound extrapyramidal symptoms, autonomic instability, and altered consciousness, is readily recognized and diagnosed. As clinicians have become more familiar with the full syndrome, however, there have been numerous observations of atypical cases that may lack one of the key features or present with only mild to moderate evidence of one or more features. Although some authors accept that these milder or atypical syndromes represent variants of NMS, others argue that the diagnosis is being used too liberally and could lead to failure to diagnose other conditions. It follows that a broadened definition of NMS could result in higher incidence rates. The variation in incidence in the studies mentioned may be partially attributable to the use of differing criteria for making the diagnosis of NMS.

One approach to resolving the question of what the incidence rate of NMS actually is would be to organize a large multicenter prospective study. It would provide the necessary numbers of patients to study this relatively rare disorder. Such a study would necessarily include clearly defined diagnostic criteria, and therefore the incidence would not be