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ARTÍCULO DE INVESTIGACIÓN

Clinical characteristics and predictors of neuroleptic malignant syndrome: A Mexican experience

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RESUMEN

Antecedentes. El síndrome neuroléptico maligno (SNM) constituye una complicación infrecuente, pero potencialmente fatal, asociada con el uso de neurolépticos (NLPs).

Objetivos. Estimar la frecuencia, presentación clínica, curso y evolución del SNM en el Instituto Nacional de Neurología y Neurocirugía MVS.

Métodos. Retrospectivamente se revisaron los casos de SNM diagnosticados entre 1990 y 1999 examinando las condiciones psicopatológicas previas al establecimiento del síndrome y las características clínicas de la presentación, tratamiento, curso y evolución de los episodios. Posteriormente, se realizó un seguimiento prospectivo (36 meses en promedio) de la evolución y la presencia de síntomas residuales.

Resultados. De un total de 4,831 pacientes expuestos a NLPs, ocho presentaron un episodio de SNM (incidencia de 0.165%). Siete casos estuvieron asociados con la administración de haloperidol. Otros NLPs asociados con la presencia de SNM fueron pipotiazina y levomepromazina. Un paciente recibió concomitantemente litio. La mayoría de los casos presentaron, previamente al establecimiento del SNM, características psicopatológicas consideradas como factores de riesgo para el síndrome, tales como agitación psicomotora, confusión, desorganización conductual y síntomas catatónicos. No se detectaron fatalidades y en sólo un paciente se reportaron secuelas, consistentes en síntomas cerebelosos y extrapiramidales, después de tres años del SNM.

Conclusiones. La frecuencia del SNM encontrada en este estudio, relativamente menor a la reportada en otros países, puede deberse en parte al advenimiento y uso de los nuevos antipsicóticos atípicos, a los estrictos criterios diagnósticos para SNM y a la poca familiaridad con el diagnóstico del SNM por parte de los médicos. La presencia de agitación psicomotora, confusión, desorganización con-

ABSTRACT

Background. *Neuroleptic Malignant Syndrome (NMS) is an uncommon but potentially fatal complication of antipsychotic and neuroleptic drug treatment.*

Objectives. *This study estimated the frequency, clinical presentation, and outcome of the NMS in a referral center for neurological, neurosurgical, and psychiatric disorders in Mexico.*

Methods. *Authors conducted a through search of psychiatry, neurology, neurosurgery, and intensive care unit (ICU) records for cases of NMS during the 10-year period between 1990 and 1999. They examined preceding psychopathological status, clinical features, course, and treatment of the NMS episodes, and performed a follow-up survey for residual symptoms and clinical outcome. The mean time to follow-up assessment was 36 months.*

Results. *A total of 8 of 4,831 neuroleptic-treated patients had an episode of NMS (incidence 0.165%). Seven of the eight patients were treated with haloperidol. Other neuroleptics agents associated were depot pipotiazine palmitate and levomepromazine. One patient received concomitantly lithium. Preceding psychopathological features such as psychomotor agitation, confusion, disorganized behavior, and catatonia postulated as clinical risk factors for the neuroleptic malignant syndrome were found in most cases. No fatal outcome was found. Only one patient developed persistent clinical sequelae, consisting of extrapyramidal and cerebellar symptoms, after three years of the NMS episode.*

Conclusions. *Psychomotor agitation, confusion, disorganized behavior, and catatonia may be potential clinical risk factor for NMS. The slightly low frequency of NMS found in this study compared to studies in other countries may be attributable to the advent and use of the newer atypical antipsychotics in Mexico, the rigorous demands for*

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ductual y síntomas catatónicos previos al establecimiento del SNM en la serie de casos estudiados fortalece el supuesto papel putativo de estos síntomas como factores de riesgo para desarrollo del SNM.

Palabras clave: Síndrome neuroléptico maligno, NMS, neurolépticos, frecuencia, factores de riesgo.

NMS diagnostic criteria and the lack of familiarity with the diagnosis between physicians.

Key words: *Neuroleptic malignant syndrome, NMS, neuroleptics, frequency, incidence.*

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a potentially fatal adverse effect of neuroleptics.[1] Since the initial description forty-two years ago [2] a large quantity of clinical data has accumulated on the manifestations, course, treatment and pathogenesis of this serious drug reaction. NMS is a rare form of neuroleptic drug-induced hyperthermia, altered level of consciousness, extrapyramidal effects, autonomic instability and muscle rigidity.[3] This dangerous condition requires early recognition, immediate discontinuation of neuroleptic treatment, intensive medical and nursing care, and search for infection or other treatable conditions.[4] Although NMS is uncommon, the widespread use of neuroleptic drugs suggests that the absolute number of cases is not insignificant. Estimates of the incidence of NMS have varied depending on the population at risk, prescribing practices and methods of assessment. Surveys of NMS in different psychiatric populations reported in various countries have yielded frequencies of 0.02 to 2.4 percent.[4-9] Heightened vigilance on the part of clinical providers has reduced morbidity and mortality caused by this disorder over the past decade.[3] To our knowledge, there are not published estimates of the frequency of NMS in Mexico. The aim of this retrospective investigation and prospective follow-up study was to determine the frequency, clinical presentation and outcome of NMS, as well as to examine the psychopathological status preceding the onset of NMS, in Mexican inpatients exposed to neuroleptics.

METHODS

A through search of psychiatry, neurology, neurosurgery, and ICU records for cases of NMS during a 10-year period was conducted. The study population consisted of 4,831 inpatients (58% males, 42% females) treated with neuroleptic agents (conventional as well as the newer atypical antipsychotics) in the National Institute of Neurology and Neurosurgery in Mexico City from January 1990 to December 1999. All those inpatients diagnosed with NMS were selected. The NMS diagnosis was re-evaluated according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV TR) research criteria (Diagnostic criteria are listed in Table 1),[10] and information from the NMS episode, such as clinical features of onset, course, treatment, and outcome, was collected. In addition, we also assessed the presence of postulated putative psychopathological risk factors, namely psychomotor agitation, confusion, disorganization, and catatonia. These symptoms were considered as present or absent based on specific

Table 1. Research criteria for neuroleptic malignant syndrome.

A. The development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.

B. Two (or more) of the following:

1. Diaphoresis
2. Dysphagia
3. Tremor
4. Incontinence
5. Changes in level of causciousness ranging from confusion to coma
6. Mutism
7. Tachycardia
8. Elevated or labile blood pressure
9. Leucocytosis
10. Laboratory evidence of muscle injury (e.g., elevated CPK)

C. The symptoms in Criteria A and B are not due to another substance (e.g., phencyclidine) or a neurological or other general medical condition (e.g., viral encephalitis).

D. The symptoms in Criteria A and B are not better accounted for by a mental disorder (e.g., Mood Disorder With Catatonic Features).

Source: Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV TR), 4th ed. Washington, D.C., American Psychiatry Association, 2000, p. 798.

definitions[11] and whether or not they were prominent in the clinical presentation of each patient. Psychomotor agitation was considered as present when severity of this symptom required mechanical restraints in one or more episodes. Confusion was rated as positive when disorientation to time and to place and/or impairment in cognition (memory, language, or attention) were predominant without an identifiable cause.

Disorganization was considered as present in case of disorganized speech (derailment, tangentiality, incoherence) and/or disorganized behavior (unusual and inappropriate behaviors or untriggered agitation). Catatonia was considered in the presence of specific motor behaviors, including negativism, mutism, rigidity, posturing, and withdrawal as part of an overall state of hypoactivity that can reach the point of stupor and/or overall state of hyperactivity (excitement, impulsivity, and combativeness).[11] Subsequently, a prospective follow-up survey for residual symptoms and clinical outcome was carried out. The study was approved by the Institutional Ethical and Research Committee.

Statistical analysis

Descriptive statistics employing measures of central tendency and measures of dispersion were calculated as appropriated.

RESULTS

Out of the total number of 4,831 inpatients treated with neuroleptic agents during the ten-year study period, 8 separate patients (3 males, 5 females) had a definite episode of NMS, for an incidence of 0.165 percent (1.65 per 1,000 cases treated with neuroleptics). There were not fatal cases. The clinical characteristics of patients with NMS are summarized in table 2.

The mean age of patients was 30 years (SD = 14.26), ranging from 17 to 56 years. The primary psychiatric diagnoses for these patients were: delirium (3/8), schizophrenia (2/8), bipolar disorder II (1/8), brief psychotic disorder (1/8), and schizophreniform disorder (1/8). The documented causes of delirium were probable viral encephalitis in two cases, and substance withdrawal delirium (dextropropoxiphene) in other one. The mean duration of primary psychiatry illness was 1.4 years (SD 1.97), ranging from 2 weeks to 5 years.

Five patients had previous exposure to neuroleptics, while for the three others it represented their first time exposition to neuroleptic agents. Neuroleptics implicated as a causative factor of NMS were: haloperidol, alone or in combination with levomepromazine or lithium (7/8), depot pipotiazine palmitate (1/8) and levomepromazine (1/8). Two patients received anticholinergic agents (Biperiden) at the time of NMS development, and one patient was treated concomitantly with lithium and haloperidol. Lithium levels in serum were in therapeutic range (0.6-1.4 mEq/L). Lithium toxicity and other causes of fever and neurologic deterioration related with lithium were ruled out.

Two patients developed NMS symptoms within 24 hours of initiating neuroleptic treatment, five by one week, and one after three weeks. Mental status changes (e.g., confusion, nervousness) were the first manifestations of the syndrome in six patients, fever in one, and rigidity in another one. Other signs presented include: sialorrhea and tachycardia (6/8); tremors, diaphoresis and tachypnea (5/8), and labile blood pressure and incontinence (3/8). One patient presented, in addition, dysarthria, dysphagia, catatonia and myoclonus, and he developed myoglobinuric renal failure, and clinical evidence of disseminated intravascular coagulation. His brain imaging studies (CT scan and MRI), cerebrospinal fluid examination and sepsis evaluation were negative, and nonfocal generalized slowing was reported on electroencephalography (EEG). Measures of serum creatine kinase were assessed only in half of the patients (4/8), and levels were found elevated at mean of 9,016 U/L (re-

Table 2. Clinical characteristics of 8 patients NMS.

Subject	Age	Gender	Primary psychiatric diagnosis	Previous exposure to NLP	Duration NMS episode (days)	Drug implicated	Mean CPK (U/L)	Follow-up assessment (mean 36 months)	
								MMSE	GAF
Case 1	27	F	Bipolar disorder II	Yes	10	HPD/Li	27,340	29	71
Case 2	26	F	Delirium	No	13	HPD	4,355	29	71
Case 3	17	F	Schizophreniform disorder	No	10	HPD	6,322	30	80
Case 4	17	M	Schizophrenia	No	15	HPD	8,774	29	61
Case 5	56	M	Schizophrenia	No	14	PPT	5,789	26	71
Case 6	25	F	Delirium	No	14	HPD/LVP	380	28	61
Case 7	24	M	Brief psychotic disorder	No	17	HPD	9,764	29	71
Case 8	48	F	Delirium	Yes	14	HPD	9,863	28	80

Note. NMS: Neuroleptic malignant syndrome; CPK: creatinine phosphokinase; NLP: Neuroleptics; MMSE: Mini-mental status Examination; GAF: Global Assessment of Functioning; HPD: Haloperidol; Li: Lithium; PPT: Depot pipotiazine palmitate; LVP: Levomepromazine chlorhydrate.

ference range= 5-270 U/L). Leucocytosis was documented in seven patients.

In terms of treatment, in addition to the discontinuation of neuroleptic medications and establishment of supportive therapies (intravenous fluids, antipyretics, etc), five patients received central cholinergic blockers (e.g., Biperiden hydrochloride), dopamine agonists (e.g., bromocriptine) and benzodiazepines (e.g., Midazolam hydrochloride and diazepam). Two patients received systemic antibiotics and prophylactic antiepileptic therapy. None received electroconvulsive therapy (ECT). All patients were treated in neurology or psychiatry services except for two patients whom were transferred to the ICU. The mean recovery time for the acute hyperthermic symptoms was estimated at 13.3 days. Six of the eight patients recovered within two weeks, and all within 30 days, including the patient who received long-acting depot neuroleptic.

In terms of the psychopathological status preceding the onset of NMS evaluating, we examined the presence of four key psychiatric symptoms (psychomotor agitation, confusion, disorganization and catatonia) in all patients (Table 3). In six patients mental status changes, characterized by confusion and nervousness, were the first manifestations of the syndrome. One patient presented with an acute and severe catatonic syndrome, in addition to all the three key psychiatric symptoms. Five patients showed fragmented, disorganized psychotic symptoms with psychomotor agitation. Two patients presented with an acute psychotic episode, with two or three key psychiatric symptoms, but not catatonia.

A prospective follow-up investigation for clinical outcome, residual symptoms, and current level of functioning was conducted in all patients. The mean time to follow-up assessment was 36 months. Physical and neurological examination, clinical evaluation using the Mini-mental status Examination (MMSE)[12] and the Structured Clinical Interview (SCID) for the DSM-IV,[13] EEG and CT scan were performed in 5 patients. The other 3 patients were contacted and interviewed by telephone using the same clinical scales.

Most of the patients recovered from NMS episode without any major complication. The total MMSE scores ranged from 25 to 30 points, and the mean score was 28.2. All patients had a Global Assessment of Functioning (GAF) > 60 (scores ranged from 61 to 80). One patient developed a residual catatonic-parkinsonian state that persisted for two months, and after 3 years of NMS episode he still showed mild but persistent extrapyramidal and cerebellar symptoms, such as intention tremor, past-pointing, disdiadochokinesia and rigidity, however no abnormalities were found in the CT scan and EEG.

Table 3. Psychopathological status preceding the onset of NMS.*

Symptom	Cases (n = 8) (%)
Psychomotor agitation	5 (62.5)
Confusion	6 (75.0)
Disorganization	5 (62.5)
Catatonia	1 (12.5)

NMS: Neuroleptic malignant syndrome.

* Presence of symptoms based on specific definitions (Berardi et al, 1998).

DISCUSSION

This study showed that of the 4,831 inpatients treated over a ten-year period with neuroleptic agents, 8 (0.165%) manifested an episode of NMS. This frequency is consistent with one previous study (Deng et al., 1990), although it is slightly low compared with the average combined incidence of NMS (0.2%) found in several large studies.[14] More than a half of the patients (5/8) had been exposed previously to neuroleptics although none had experienced a similar episode during prior treatments. In all cases doses of neuroleptics were within the therapeutic range. The most frequent antipsychotic employed was haloperidol (7/8) alone or in combination, and the most frequent route of administration was parenteral (6/8). The dosage range of haloperidol was between 5 and 20 mg per day. The fact that three patients were exposed for he first time to neuroleptics, and seven were treated with haloperidol may suggest that previously untreated patients and those treated with high-potency neuroleptics are at major risk to develop NMS.[15]

The use of haloperidol as frequent first-line therapy, a common trend among Mexican psychiatrists during the nineties,[16] may explain the high frequency (7/8) of patients with NMS treated with haloperidol in our sample. Even though data about whether adjunctive or concomitant medications (e.g., antiparkinsonian drugs or lithium) increase the risk of NMS are inconclusive,[17] there is a general consensus that combinations of psychotropics may contribute to the risk of NMS. In our sample, four patients received more than one psychotropic; three patients received concomitant anticholinergic agents (e.g., biperiden), one received lithium, and other received two neuroleptics simultaneously.

Psychomotor agitation, confusion, disorganization, and catatonia were characteristic symptoms in the pre-NMS presentation in our case series, which is consistent with previous reports that raise the possibility that they are risk factors for the syndrome.[11] All cases presented with an acute psychotic episode before the onset of the syndrome, in which

Table 4. Differential diagnosis of NMS

Primary brain disorders
Infections, tumors, trauma, status epilepticus, strokes, idiopathic lethal catatonia, serotonin syndrome
Systemic disorders
Infections, toxins, heatstroke, dehydration, endocrinopathies, drugs autoimmune disorders

Table 5. Medical and neurologic evaluation of possible NMS.

Basic
Physical examination
Electrolytes, including calcium and magnesium
Renal and hepatic function tests
Complete blood count
Serial tests of creatine phosphokinase levels
Urinalysis
Lumbar puncture
Computed tomography or magnetic resonance imaging scan of the head
Optional
Arterial blood gases
Coagulation studies
Blood cultures
Toxicology screen
Lithium level
Iron deficiency tests

Adapted from: Pelonero et al., 1998.

fragmented psychotic symptoms and disorganized speech and behavior were characteristic. Catatonic symptoms (present in one case), antecedent to neuroleptic administration, have been described previously.[17,18] However, the fact that quantitative rating scales were not used to measure the severity of psychomotor agitation, confusion, disorganization, and the dimension of the sample, limit the interpretation of these findings.

No fatal cases were identified, and most of the patients recovered from NMS episode without any life-threatening complication. Only one patient developed persistent clinical sequelae after three years, which is consistent with other previous reports.[19]

The slightly low frequency of NMS in our sample may be at least partially attributable to the advent and use of the newer atypical antipsychotics in Mexico,[16] or to rigorous demands for NMS diagnostic criteria. In the other hand, because the disorder is too infrequent and idiosyncratic, physicians may not be familiar with the diagnosis. In addition, a broad range of conditions may resemble NMS (Table 4), thus the differential diagnosis of NMS is challenging and include many disorders presenting with fever, necessitating a through medical and neurologic evaluation. In some patients, despite meticulous investigation, the cause of NMS may remain obscure or the diagnosis NMS elusive (Table 5). Therefore, the possibility exists that milder cases of NMS were not diagnosed and hence not included in the study. Finally, the methodological flaws inherent to the retrospective design of this study (e.g., completeness and accuracy of medical records) must be considered. Also, quantitative rating scales were not used to measure the severity of psychomotor agitation, confusion, disorganization, and lastly the dimension of the sample, which could be insufficient in the identification of possible risk factors.

Recognition of this condition is essential because its complications are potentially lethal. More large-scale prospective studies including more clinical and laboratory data on non-NMS neuroleptic-treated patients as well as patients with mild and moderate forms of NMS are needed to refine the frequency of NMS in Mexican population. Multicenter case-control studies, as suggested by Deng et al,[5] which would improve statistical reliability by increasing sample size, thereby enabling better definition of the risk factors involved in the development of this severe complication of treatment with neuroleptics.

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