Article

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Neuroleptic malignant syndrome

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is a potentially fatal adverse event associated with the use of antipsychotics (AP). The objective of this study was to investigate the profile of cases of NMS and to compare our findings with those published in similar settings. A series of 18 consecutive patients with an established diagnosis of NMS was analyzed, gathering data on demography, symptoms and signs. Two thirds of all cases involved woman with a past medical history of psychiatric disorder receiving relatively high doses of AP. The signs and symptoms of NMS episodes were similar to those reported in other series and only one case had a fatal outcome, the remaining presenting complete recovery. As expected, more than two thirds of our cases were using classic AP (68%), however the clinical profile of these in comparison with those taking newer agent was similar. Newer AP also carry the potential for NMS.

Key words: atypical antipsychotics, typical antipsychotics, neuroleptic malignant syndrome.

Síndrome neuroléptica maligna

RESUMO

A síndrome neuroléptica maligna (SNM) é um evento adverso potencialmente fatal associado ao uso de antipsicóticos (AP). O objetivo deste estudo foi investigar as características clínicas de cases da SNM e comparar nossos resultados com os publicados na literatura. Uma série de 18 pacientes com diagnóstico confirmado de SNM foram analisados, associando dados demográficos, apresentação clínica, diagnóstico e tratamento. Dois terços dos casos envolveram mulheres com antecedentes psiquiátricos que recebeceram doses relativamente altas de AP. Os sinais e sintomas foram semelhantes àqueles já relatados na literatura e a maioria dos pacientes teve uma recuperação completa, exceto por um caso com desfecho fatal. Houve predomínio de pacientes que usam medicamentos neurolépticos clássicos (68%), porém não houve diferença nas manifestações destes casos em relação àqueles que usavam AP novos. AP mais novos também têm o potencial de causar SNM.

Palavras-Chave: neurolépticos atípicos, neurolépticos típicos, síndrome neuroléptica maligna.

Neuroleptic malignant syndrome (NMS) is a drug-induced, idiosyncratic condition that was first described by Delay et al.[1] in 1960 with the use of haloperidol. NMS is classically associated with the use of high-potency antipsychotics (AP), such as butyrophenones and phenothiazines, but has also been described with newer agents, commonly described as "atypical" AP (risperidone, olanzapine, quetiapine), other D2-receptor antagonists (metoclopramide) and following withdrawal of anti dopaminergic agents[2-19]. Although the precise pathophysiologic mechanism underlying NMS remains unknown, a reduction in dopaminergic activity in the brain probably by dopamine D2 receptor blockade in the striatum and hypothal-

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amus is generally assumed as a potential cause[4,20]. NMS is characterized by a distinctive clinical tetrad of mental status changes, motor abnormalities (bradykinesia and muscle rigidity), autonomic dysfunction (blood pressure instability, diaphoresis and tachycardia), and hyperthermia[2-5]. Laboratory findings include elevation of serum creatine phosphokinase (CK), liver enzymes, and leukocitosis[2-7,21]. Estimates of the incidence of this syndrome ranges from 0.01 to 3.23 accordingly to diagnostic criteria and drug prescription practices[3,4,6,22]. Mortality is estimated at about 10%[3,4,23,24]. Treatment is mainly supportive and includes withdrawal of the AP or other causative agent, and occasional use of drugs such as dopaminergic agonist (bromocriptine) and dantrolene[2-4,25-28].

Herein we describe a series of 18 Brazilian cases and a practical review of literature of this life-threatening condition.

METHOD

This was a cross sectional study including 18 patients with NMS admitted at the Neurology Service, Hospital de Clínicas of the Federal University of Paraná and the Neurology Service of the Pontifical Catholic University of Paraná, Brazil. Data were collected using a standardized protocol from 1985 to 2010 by two examiners (HAGT, RPM). Patients were included only after the definitive final diagnosis was established. Those with dubious or incomplete diagnostic criteria for any final diagnosis were not included. The diagnosis of NMS was based in the Levenson's criteria, published in 1985[2].

Autonomic dysfunction signs or symptoms included variation in systemic blood pressure, tachycardia, tachypnea, sialorrhea, diaphoresis, skin pallor, and urinary incontinence. Additional variables included demographic data, causative agent, clinical manifestations, paraclinical findings, therapy, and clinical outcome. Previous medical history, potential risk factors, and history of recent use of AP were also investigated. Causative agents were divided as classic or newer AP (Table 1).

RESULTS

The overall sample included 12 (66.67%) females. Mean age was 49.5±10 years (range: 18 to 81). Five had the diagnosis of schizophrenia, four had bipolar disorder, three had dementia (Parkinson's disease dementia, Lewy body dementia and Alzheimer's disease), two had delirium, two had encephalitis after bone marrow transplantation, one had systemic lupus erythematosus related psychosis, one had psychosis in the course of multiple sclerosis (Table 1). Thirteen (72.23%) were taking one potentially causative drug. Five (27.78%) were using more than one, including three cases in which two drugs were used concomitantly, one using three drugs, and one case in which four drugs were used concomitantly. In the sample of 18 cases there were 25 citations of agents (Table 2), including 7 different drugs. Haloperidol was the commonest, accounting for 10 citations, followed by risperidone in 5, chlorpromazine in 3, levomepromazine and olanzapine both in 2, and thioridazine and quetiapine both in 1 case. Eight patients were taking newer agents (risperidone, olanzapine, and quetiapine). All cases were related to introduction of the drug or dose increase in the past 3 months. Three patients were using biperiden, and carbonate lithium combined with an AP. Clinical presentation was diverse across the whole series, however the onset in all cases included altered mental status (agitation or apathy) and rigidity, follow by hyperthermia, the most common dysauthonomic sign (Table 1).

Laboratory tests showed significant increase in serum CK in all patients, elevated creatinine in 11 (61.1%) patients and leukocytosis with left shift in 11 (61.1%) cases. Screening for infectious diseases and other potential confounding conditions was performed in dubious cases, displaying negative results. Treatment interventions included withdrawal of the AP, supportive care and pharmacologic treatment. Seven (38.9%) patients received bromocriptine and the 11 (61.1%) other drugs, including, amantadine, levodopa, diazepam, and pramipexole. A fatal outcome occurred in one case (5.5%) (Table 1).

DISCUSSION

This case series includes the experience of two tertiary Brazilian centers of adult neurology, thus underlining how uncommon and possibly underreported this potentially fatal neurological emergency is. Although the diagnosis of NMS can be challenging, an estimated 0.5-1% of patients exposed to AP will develop this syndrome[1,2]. Most patients will develop it shortly after initial exposure and 90% within two weeks of starting the AP. Much less commonly, NMS can occur after sudden discontinuation of the drug therapy.

As already underlined, the most common causative agents are high potency typical AP and, occasionally, newer "atypical" AP, including risperidone, clozapine, olanzapine and quetiapine. In our sample, 32 % were taking this later class of AP, a figure not as low as in other series, probably accounted for by local prescribing practices. Of importance, there seems to be no difference regarding the clinical and paraclinical manifestations in cases using either classic or newer AP. The underlying neuropsychiatric diagnoses are typically schizophrenia and affective disorders, but NMS also occurs among patients with other conditions for which AP are used, including dementia, delirium, other psychoses, mental retardation, and Parkinson's disease[3,4,29]. Also, as the majority of cases will eventually require the use of AP to

Table 1. Clinical and laboratory data of 18 patients with NMS.

Case	Gender	Age	Diagnosis	Previous medication	Altered mental status	Muscular rigidity	Temp	Dysautonomia	Leukocytosis	CK Elevate	Creatinine	Treatment	Outcome
1	F	18	SLE/DEM	Haloperidol	+	+	40	+	+	+	3.5	Bromocriptine	Improve
2	F	63	Delirium	Haloperidol, Lithium, Biperiden	+	+	38.5	+	–	+	3.1	Bromocriptine	Improve
3	M	46	PD/DEM	Haloperidol	+	+	41.5	+	+	+	1.2	Amantadine, Levodopa, Diazepam	Improve
4	M	38	BPD	Chlorpromazine, Levomepromazine, Thioridazine, Biperiden	+	+	37.9	+	–	+	1.3	Levodopa	Improve
5	F	26	Schizo	Haloperidol, Levomepromazine, Biperiden	+	+	38.9	+	+	+	5.0	Levodopa	Improve
6	F	81	Delirium	Risperidone	+	–	39	+	+	+	NL	Bromocriptine	Improve
7	M	45	BPD	Haloperidol	+	+	39	+	+	+	NL	Bromocriptine	Improve
8	F	68	LBD/DEM	Quetiapine	+	+	40	+	+	+	1.2	Pramipexole, Levodopa	Improve
9	F	78	AD/DEM	Risperidone	+	+	40	+	+	+	1.5	Levodopa, Pramipexole	Improve
10	M	30	Encephalitis	Haloperidol	+	+	39	–	–	+	1.2	Bomocriptine	Improve
11	M	27	Encephalitis	Haloperidol	+	+	41	+	–	+	1.4	Bromocriptine	Improve
12	F	49	Schizo	Carbamazepine, Risperidone	–	–	41.2	+	–	+++	NL	Midazolam, Amantadine, Clonidine	Death
13	F	51	MS	Carbamazepine, Diazepam, Chlorpromazine	+	+	40	+	NI	+	1.6	Amantadine, Diazepam	Improve
14	F	65	BPD	Olanzapine, Lithium	+	+	38	–	+	++	NL	Bromocriptine, Amantadine	Improve
15	F	27	Schizo	Risperidone, Haloperidol, Chlorpromazine, Olanzapine	+	+	38.2	+	+	+	NL	Clozapine, Amantadine	Improve
16	F	39	Schizo	Haloperidol, Clonazepam, Valproate	+	+	41.8	+	–	+++	NL	Amantadine, Levodopa	Improve
17	F	23	BPD	Lithium, Risperidona, Haloperidol, Clonazepam	+	+	39	+	+	+++	2.25	Amantadine, Levodopa, Pramipexole	Improve
18	M	34	Schizo	Diazepam, Midazolam, Haloperidol, Clonazepam	+	+	38.5	+	+	+++	NL	Amantadine, Pramipexole	Improve

F: female; M: male; SLE: Systemic Lupus Erythematosus; Dem: dementia; PD: Parkinson's disease; BPD: bipolar disorder; Schizo: schizophrenia; LBD: Lewy Body Dementia; AD: Alzheimer's disease; MS: multiple sclerosis; Temp: temperature (maximum) - Celsius degree; Dysautonomia (labile blood pressure, hyperthermia, sialorrhea, diaphoreis, tachycardia); +: present; –: absent; NI: not informed; Leukocytosis: –: 0-10.000; +: 10.000-20.000; ++: >20.000; CK: creatine kinase (–: 0-100 U/L; +: 100-500 U/L; ++: 500-1000 U/L; +++: >1000 U/L); Creatine: NL: normal (+: ≥1.2 mg/dL).

Table 2. Drugs related to drug-induced neuroleptic malignant syndrome.

Drug class	n
Typical neuroleptic	17
Haloperidol	11
Levomepromazine	2
Chlorpromazine	3
Thioridazine	1
Atypical neuroleptic	8
Risperidone	5
Quetiapine	1
Olanzapine	2
Total	25

control their underlying psychiatric disorder, the safest approach for prevention of recurrence is the use of slowly titrated lower potency agents[30]. In the series presented here, two thirds of all cases involved women with a past medical history of either psychiatric disorder and, less commonly, dementia, receiving relatively high doses of both classic and newer AP. Common predisposing factors include a prior episode of NMS, dehydration, agitation, poor oral intake, elevated ambient temperature, emotional stress, humidity and concomitant use of lithium, anticholinergic agents or some antidepressants[4,7,31,32].

In a review of 202 case reports, Shalev et al.[24] noted a decreasing mortality trend, occurring in 11.6% after 1984, while 25 % of cases had a fatal outcome when diagnosed before 1984. This is probably attributable to better recognition of the syndrome with earlier intervention. In this case review, patients with NMS with organic mental disorders had significantly higher mortality rates, as did patients who developed myoglobinuria and renal failure[3]. In our study we had one patient (5.5%) with a fatal outcome, similar to the mean 5% described in more recent series of NMS[4]. Also, in our series, all the remaining patients made a full recovery, however the literature shows that some patients may be left with permanent parkinsonism, ataxia, and dementia[4,11]. Mortality and morbidity associated with NMS can be further reduced by increased awareness of its initial clinical symptoms and signs, allowing for prompt clinical menagement[33]. Newer agents, typically regarded as safe, are also not uncommonly related to NMS and the use of these AP should not preclude diagnostic suspicion[4,11,14-17].

NMS must be differentiated from other similar syndromes such as malignant hyperthermia, serotonin syndrome, and catatonia[4,34].

In conclusion, NMS is a potentially fatal adverse event associated with the use of AP characterized by severe rigidity, tremor, fever, altered mental status, autonomic dysfunction, and elevated serum creatine phosphokinase and white blood cell count. In our series of 18 patients with NMS the signs and symptoms were similar to those reported in other series and only one case had a fatal outcome, the remaining presenting complete recovery. As expected, more than two thirds of our cases were using classical AP (68%), however the clinical profile of these in comparison with those taking newer agent was similar. Given the widespread use of AP, all prescribing physicians should be able to identify and early in its course. Newer AP also carry the potential for NMS.

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