NEUROLEPTIC MALIGNANT SYNDROME

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Neuroleptic malignant syndrome is a life-threatening reaction of neuroleptic medication. The estimated incidence rate of neuroleptic malignant syndrome is between 1% and 1.5% of patients treated with neuroleptics. The reported mortality rate varies from 11% to 38%. Risk factors include younger males (80% less than 40 years) and physical disability.

Although 80% of neuroleptic malignant syndrome cases develop within the first 2 weeks of treatment, the syndrome can develop anytime during the therapy period. The clinical picture and laboratory findings are not always unique. Less than 50% of cases manifest with classical symptoms. Deaths usually result from cardiovascular collapse. Renal failure, pulmonary emboli, aspiration pneumonia, and respiratory failure are also reported.

Familiarity with the syndrome, baseline laboratory values including creatine phosphokinase, lactate dehydrogenase, serum glutamic-oxaloacetic transaminase, and complete blood cell count with a differential count, and a high index of suspicion are of the utmost importance in making the diagnosis of neuroleptic malignant syndrome. A judicial choice of neuroleptic medication and careful observation of patients may reduce the incidence, morbidity, and mortality of neuroleptic malignant syndrome. (*J Natl Med Assoc.* 1992;84:966-970.)

Key words • neuroleptics • neuroleptic malignant syndrome • antipsychotics • bromocriptine

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Neuroleptic malignant syndrome is a complex, acute, life-threatening reaction to neuroleptic medication, characterized by the following signs and symptoms: fever, muscle rigidity, catatonic state, altered consciousness, autonomic instability, tremor, dyskinesia, akinesia, oculogyric crisis, opisthotonos, and chorea. Dysarthria, dysphagia, sialo-pneumonia, Babinski's signs, and generalized tonic-clonic seizures are also seen.[1,2]

The estimated incidence rate of neuroleptic malignant syndrome ranges between 1% and 1.5% of patients treated with neuroleptic medications.[1,3-6] However, the incidence rate is underestimated. The average reported mortality ranges from 11% to 38%.[1-8]

The offending agents include phenothiazine and other antipsychotics, carbamazepine, lithium salts, and L-dopa.[9,10] Haloperidol and fluphenazine are the most frequent drugs involved in causing neuroleptic malignant syndrome (Table 1).

Risk factors include younger males (80% of males with the syndrome are under the age of 40 years) with a male:female ratio of 2:1. Certain physical factors such as organic brain syndrome, dehydration, nutritional deficiencies, physical exhaustion, and heat stress may enhance the development of neuroleptic malignant syndrome.[2]

Schizophrenic patients constitute about 50% and bipolar affective patients consitute about 25% of the patients who suffer from neuroleptic malignant syndrome.

Clinical presentation includes the following core symptoms and signs:

- fever, often >40°C (>104°F) (although hyperthermia has been called the cardinal sign of neuroleptic malignant syndrome, it may not be present in all cases),
- severe muscle rigidity, "lead pipe" or plastic type even at times catatonic state as opposed to "cog-wheel" rigidity usually seen in Parkinsonism,[1]

TABLE 1. DRUGS RESPONSIBLE FOR NEUROLEPTIC MALIGNANT SYNDROME*

%	Drug
50 to 60	Haloperidol
25	Fluphenazine
15 to 25	Chlorpromazine
	Prochlorperazine
	Trifluoperazine
	Perphenazine
	Thioridazine
	Molindone
	Lithium
	Carbamazepine
	Centrally acting drugs that affect dopamine levels such as L-dopa

*Based on references 1-10.

TABLE 2. AIDS TO DIAGNOSING NEUROLEPTIC MALIGNANT SYNDROME

Elevated Creatine Phosphokinase Level
Level ranges between 2000-15 000 U/L in 40% to 50% of cases; in some cases, the level may vary from <2000 to 100 000 U/L

Leukocytosis
14.5 to 30 K/cu mm with a shift to the left in about 40% of cases

Liver Function Tests
Liver enzyme elevation also may be present, especially elevated lactate hydrogenase and serum glutamic-oxaloacetic transaminase levels

Electroencephalogram
Electroencephalograms are not diagnostic; they may be normal or may show diffuse slowing

- altered consciousness from clouding sensorium to stupor or coma, and
- autonomic instability, manifested by labile pulse and blood pressure, diaphoresis, tachypnea, and pallor.

All four symptoms and signs may not be present in every case, which probably relates to the under diagnosis of this potentially life-threatening but treatable syndrome. Table 2 presents several aids to diagnosing neuroleptic malignant syndrome.

In about 80% of the cases, neuroleptic malignant syndrome develops within the first 2 weeks of initial treatment. However, it should be noted that neuroleptic malignant syndrome can occur any time during treatment with the offending drugs, most often after an increase in the dose. Initially, labile vital signs may preclude the syndrome by 3 to 5 days, then progress rapidly to full-blown syndrome in 24 to 72 hours. The syndrome lasts about 12 to 14 days but may last up to 30 days. When depot agents are involved, it can last two to three times longer.[1]

CASE REPORTS

Case 1

A 63-year-old divorced fully ambulatory white male was transferred from the medical ward to the psychiatry ward in January 1989 for further evaluation of his neuropsychiatric illness. He had originally been admitted to the medical ward for alcohol-related withdrawal seizures. The patient's history included a diagnosis of chronic obstructive pulmonary disease, heart failure, seizure disorders, schizophrenia (chronic paranoid type), alcohol abuse, and dementia. His medications included theophylline, phenytoin, verapamil, and lithium.

A review of the patient's medical records revealed that he had been treated for schizophrenia and "manic depressive psychosis" in the early 1970s with different neuroleptics and lithium. He was also given a diagnosis of dementia in the late 1970s secondary to ethanol abuse.

During the last week of January 1989, haloperidol (2 mg twice a day) and benztropine (1 mg twice a day) were added to his medications because of agitation. The haloperidol was subsequently increased to 2 mg three times a day but discontinued after the patient developed a dystonic reaction. During the first week of February 1989, he was started on fluphenazine (5 mg three times a day and 5 mg every 2 hours as needed). Benztropine was discontinued, and an anti-Parkinsonian drug, amantadine (100 mg twice a day) was added to his medications. However, the patient remained agitated. A noncontrast computed tomographic scan of the head revealed mild cerebral atrophy, but was otherwise normal. Total creatine phosphokinase at this time was only 60 U/L. During the first week of March 1989, fluphenazine was reduced to 2.5 mg three times a day, and amantadine was discontinued after adding diphenhydramine (25 mg) at bedtime. However, a few days later, fluphenazine was increased back to 5 mg three times a day.

The patient was transferred back to the medical ward during the second week of March following a seizure episode accompanied by shortness of breath. He was managed with antibiotics, prednisone, phenytoin, and phenobarbital. Fluphenazine was increased from 5 mg three times a day to 10 mg three times a day. After a few days, it was decreased back to 5 mg three times daily.

A benzodiazepine (lorazepam) was used as needed to control the patient's agitation. Once it was reduced, he was transferred back to the psychiatry ward. Lithium (300 mg three times daily) was continued until May 30; at that time, it was discontinued because of poor clinical response despite the fact that therapeutic levels were normal. In July 1989, the patient was transferred to the surgical ward for small bowel obstruction. After surgery, he recovered uneventfully and was transferred back to the psychiatry ward. At that time, the patient's creatine phosphokinase level was 42 U/L; serum glutamic-oxaloacetic transaminase level, 23 U/L; lactate dehydrogenase level, 417 U/L; and white blood cell count, 5.8 K/cu mm.

Until the middle of November 1989, the patient was ambulatory, fairly cooperative, and took care of his activities of daily living. At that point he became more confused, disoriented, restless, and agitated. His speech became irrelevant and incoherent. His extremities became rigid (lead pipe type). At this time, vital signs revealed a temperature of 101.5°F, a pulse rate of 124/minute, a blood pressure of 118/70 mm Hg, and a respiration rate of 20/minute. His blood pressure increased to 146/96, his pulse to 126/minute, and his respiration rate to 22/minute. He became progressively diaphoretic, catatonic, sialhorric, and stuperous. Laboratory studies revealed the following values: creatine phosphokinase, 5603 U/L with MB fraction (cardiac muscle) 24 U/L; lactate dehydrogenase, 1138 U/L; serum glutamic-oxaloacetic transaminase, 105 U/L; and white blood cell count, 14.5 K/cu mm.

A neurology consultation confirmed the diagnosis of neuroleptic malignant syndrome, and the patient was subsequently transferred to the medical intensive care unit. Neuroleptics were discontinued, and bromocriptine (5 mg twice a day) was started. Within a few weeks, the patient became less confused, his muscle rigidity decreased, and he became autonomically stable. Laboratory reports disclosed the following levels: creatine phosphokinase, 40 U/L; lactate dehyrdogenase, 431 U/L; serum glutamic-oxaloacetic transaminase, 56 U/L; and white blood cell count, 6.8 K/cu mm. The patient was transferred back to the psychiatry ward in the last week of December 1989. Bromocriptine was discontinued at that time, and the patient became alert and oriented to person and place.

Case 2

A 46-year-old single white male was admitted to the psychiatry ward in June 1989 with symptoms of severe depression, hypersomnolence, head banging, and an ataxic gait. The patient had been well until 3 weeks prior to admission and was on lithium and carbamazepine. The patient had a history of prior admissions and had been diagnosed with major depression (recurrent) with psychotic features. He was treated in the past with tricyclic antidepressants, neuroleptics, and electroconvulsive therapy, and had been described to be refractory to conventional treatment. The patient had no known allergies but had a history of dystonic reactions secondary to haloperidol. He denied any substance or alcohol abuse. Lithium and carbamazepine toxicities were ruled out during the current admission. He was started on a combination of lithium, antidepressants, and haloperidol. After the patient's condition failed to improve, electroconvulsive therapy was started.

On August 1, after seven electroconvulsive therapies, the patient developed a fever of 101.8°F and became agitated. He kept rocking his head and mumbling continuously, and was found to be somewhat stiff. At this time, a complete blood cell count showed leukocytosis of 15 K/cu mm with 80% granulocytes. Urine analysis showed red blood cells and bacteria. The patient was started on antibiotics. On August 4, his fever rose to 103°F, and he became very rigid and completely mute. He was transferred to the medical intensive care unit. A computed tomographic scan of the head was negative, and meningitis was ruled out. Physical examination was remarkable for generalized rigidity and autonomic instability. There was little or no response to painful stimuli, and laboratory reports revealed a white blood cell count of 19 K/cu mm, a lactate dehydrogenase level of 856 U/L, and a creatine phosphokinase level of 1822 U/L with an MB level of 16 U/L. A diagnosis of neuroleptic malignant syndrome was made, and the patient was treated with bromocriptine (5 mg twice daily) and amantadine (100 mg twice daily). Body temperature and muscle rigidity returned to normal within 3 to 4 days.

After 1 week, bromocriptine was decreased to 2.5 mg twice daily. Laboratory data showed a normal complete blood cell count, a lactate dehydrogenase level of 561 U/L, and a total creatine phosphokinase level of 43 U/L. Once the patient was transferred back to the psychiatry ward, bromocriptine and amantadine were discontinued. Four weeks after returning to the psychiatry ward, electroconvulsive therapy was restarted. Later, he was put on trifluoperazine (5 mg/day); this dosage was gradually increased to 15 mg/day. The patient remained stable and was discharged.

DISCUSSION

Neuroleptic malignant syndrome was first described in

the late 1950s but has only recently received serious attention. The mortality has decreased from an average of 22% in cases reported before 1980 to 4% in cases reported since then, probably as a result of increased awareness, early recognition, and prompt intervention.[11]

It has been suggested that dopamine blockade within the hypothalamus is a fundamental requirement for the development of neuroleptic malignant syndrome.[4] Once dopamine blockade occurs in the thermoregulatory center of the hypothalamus, a disruption of core temperature regulation induces fever.[12] Kaufman and Wyatt postulate that "Striatal dopamine receptor blockade could cause centrally mediated muscular rigidity."[13] Dopamine is an inhibitor of thoracolumber sympathetic outflow, thus blockade would allow increased sympathetic tone and possible autonomic instability.[14] Blockade of corticolimbic dopaminergic transmission could account for mental status changes.[15]

The initial treatment for neuroleptic malignant syndrome is discontinuation of the neuroleptic and prompt initiation of supportive care. Several studies have reported variable success with the use of anticholinergics, electroconvulsive therapy, benzodiazepines, and propranolol.[7,16-20] Dantrolene sodium (a direct-acting skeletal muscle relaxant) has been reported to be effective in reducing symptoms in some patients.[20-23] Amantadine and bromocriptine, both dopamine agonists, have been beneficial in treating neuroleptic malignant syndrome, probably secondary to their relief of central dopaminergic blockade. Bromocriptine, via postsynaptic dopamine-receptor stimulation, could theoretically reduce fever, muscle rigidity, autonomic instability, and changes in mental status.[24]

Although Levenson,[8] in his review of 50 neuroleptic malignant syndrome cases, found no difference in the course of patients receiving dantrolene or bromocriptine compared with those who did not. However, bromocriptine definitely helped us manage the cases reported here.

Neuroleptic malignant syndrome is a treatable disorder. Health-care professionals, especially psychiatrists and nurses, need to be familiar with the diverse symptoms of this syndrome. Initial laboratory values, vital signs, symptoms, and a careful neurophysical examination are the cardinal tools to diagnosing neuroleptic malignant syndrome. However, as shown in the cases reported here, not all of the cardinal symptoms and signs may be present in all cases of neuroleptic malignant syndrome. Leukocyte and total creatine phosphokinase levels may not always be elevated. One can compare and contrast laboratory reports only if baseline values are known.

Many patients with a history of neuroleptic malignant syndrome (such as the patient in our second case report) have been restarted on antipsychotic drugs without any ill effects.[24] A history of neuroleptic malignant syndrome should not be considered a contraindication for future neuroleptic treatment. However, it is advised that reintroduction may be best undertaken at least 2 weeks after complete resolution of the syndrome.[24]

CONCLUSION

A judicial choice of neuroleptic medication, familiarity with the syndrome, baseline laboratory values (complete blood cell count, urine analysis, creatine phosphokinase level, lactate dehydrogenase level, and serum glutamic-oxaloacetic transaminase level), a high index of suspicion, and prompt intervention are of the utmost importance in diagnosing neuroleptic malignant syndrome.

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continued from page 950

CME is a popular method for practicing physicians to obtain CME credits.[4] Formal CME is often teacher-oriented and too little focused on what physicians actually do in their practices.[5] A number of techniques have been used to assess CME needs of physicians. Such assessment may be based on objective testing of knowledge,[6] on experts' opinions,[7] on disease incidence in the community,[8] on audit,[9] and on physician practice profiles.[10] Other methods of needs assessment include peer review, mortality and morbidity statistics, advances in medical diagnosis and techniques, quality assurance data, and demonstrated needs and wishes of community physicians.

We approach the latter method of needs assessment by the use of surveys as the tool. The survey described here is only one of many we have conducted to assess the needs and wishes of community physicians for CME. Our example illustrates the successful use of a survey as a tool for CME needs assessment. Many of our CME programs are planned, organized, and implemented by making full use of the information provided by the survey questionnaire respondents. The success of this method is proven by the number of registrants and participants at the program, their evaluative comments, and the high return rate of physicians and success of subsequent programs on similar topics.

Throughout the industry, only approximately 5% of survey questionnaires are returned following a single mailing. Although this figure is discouragingly low, the information needed to plan and successfully carry out a CME program is usually clearly stated in the survey responses that are returned.

Hospitals have traditionally been one of physicians' favorite places to receive CME. The ACCME would like to see hospitals use quality assurance data as part of CME planning more frequently.[11] Physicians must learn how to define their own CME needs. As more CME shifts from the traditional lecture format to interactive methods such as panels, workshops, and discussion groups, it is imperative to focus on needs assessment.

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continued on page 987