Neuroleptic malignant syndrome

An unusual cause of fever[1]

William H. Shafer, M.D.
Anthony J. Furlan, M.D.

The use of neuroleptic drugs may result in an acute multisystem disorder characterized by fever, leukocytosis, and extrapyramidal signs. This has been termed the neuroleptic malignant syndrome. A case is reported that illustrates many of the problems in diagnosis and management of this syndrome.

Index terms: Fever • Neuroleptic malignant syndrome

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The neuroleptic malignant syndrome, an uncommon reaction to neuroleptic drugs, was described in 1960 by Delay et al.[1] A similar syndrome has been reported to occur following the withdrawal of levodopa therapy.[2] Features of this syndrome include extrapyramidal signs, fluctuating consciousness, fever, leukocytosis, and elevated levels of muscle and liver enzymes.[3] Patients who have this reaction may become seriously ill with pulmonary complications. Renal failure from myoglobuinuria[4] has also been reported. The mortality rate may be as high as 20%. Appropriate treatment produces a rapid reversal of the illness. Because this syndrome is not well known to general physicians, we report the following case.

Case report

A 63-year-old man was transferred from a psychiatric hospital to the Internal Medicine Service of the Cleveland Clinic Hospital. One month earlier he had been admitted to the psychiatric hospital for severe depression and had received a course of electroshock therapy. Electroshock therapy was terminated when atrial fibrillation and congestive heart failure developed. During this time the patient had received doxepin, thioridazine, and thiothixene, all of which were discontinued. Heart failure was treated with digoxin and furosemide. Because of abusive behavior, haloperidol 5 mg four times a day, benztropine mesylate, and diphenhydramine were given to the patient. Forty-eight hours prior to transfer, the patient became somnolent and febrile. Because of fever, heart failure, and change in mental status, he was transferred to the Cleveland Clinic Hospital. Examination on admission disclosed a blood pressure of 160/70 mm Hg, temperature 38.7 °C, pulse 84/min and irregular. The patient was somnolent, but he could be aroused and was oriented. There was severe generalized cogwheel rigidity, a pill-rolling tremor of the extremities, and a stiff neck. There were a few scattered rhonchi throughout both lung fields.

A chest radiograph was normal. The electrocardiogram showed atrial fibrillation with runs of atrial flutter. A complete blood count showed a hemoglobin level of 16.1 g/dL and a white blood cell count of 13,900 with a differential count of 75 polymorphonuclear leukocytes, 8 bands, 7 lymphocytes, and 10 monocytes. Urinalysis showed 8–10 white blood cells and was otherwise normal. Cultures of blood, urine, and sputum were sterile. Cerebrospinal fluid analysis was normal and cultures were sterile. Laboratory studies with abnormal results included creatinine phosphokinase 1,600 IU/L, 98% skeletal muscle, SGOT 68 IU/L, LDH 372 IU/L, and creatinine 2.0 mg/dL. Digoxin levels were nontoxic.

[1] Departments of Internal Medicine (W.H.S.) and Neurology (A.J.F.), The Cleveland Clinic Foundation. Submitted for publication Dec 1985; accepted April 1986. ht

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Haloperidol was discontinued and benztropine mesylate 2 mg b.i.d. was given, along with intravenous fluids and pulmonary physical therapy. Within 36 hours the temperature was 40 °C and nafcillin 2 g q 6 hours and tobramycin 120 g q 8 hours were administered. The fever continued, however, and when the cultures remained sterile, antibiotics were discontinued after 48 hours.

The patient's fever began to abate after five days. The patient was examined by both psychiatric and neurologic consultants. A diagnosis of neuroleptic malignant syndrome was suggested and carbidopa-levodopa 10-100 mg four times a day was added to the medical program. The patient continued to improve and within 48 hours was afebrile; by the twenty-first day the extrapyramidal signs were no longer present. The confusion and somnolence cleared and there was no overt psychosis. The patient's abnormal blood chemical levels returned to normal. The atrial fibrillation reverted spontaneously to normal sinus rhythm. The patient remained free of any evidence of congestive heart failure, and was discharged from the hospital on the twenty-first day.

Discussion

Our patient had many of the manifestations of the neuroleptic malignant syndrome. The extrapyramidal complications of neuroleptic drugs are well known to physicians, but fever, altered consciousness, leukocytosis, and elevated muscle and liver enzyme levels are less familiar. Haloperidol has been the most commonly implicated of the neuroleptic drugs.[5]

The onset of this syndrome may come within hours or months of using neuroleptic drugs. Preexisting dehydration, exhaustion, brain disease, and concomitant use of lithium may be contributing factors. Progression of the illness from onset to severe extrapyramidal signs, stupor, coma, and fever may occur rapidly over 24–72 hours. Withdrawal of the drug and administration of supportive care may result in improvement over a five to 15-day period. Death has most commonly occurred from pulmonary failure. Laboratory studies may show elevated muscle creatinine phosphokinase, abnormal liver function tests, leukocytosis, and myoglobinuria. The clinical picture may suggest central nervous system infection, systemic sepsis, or vasculitis with multiple system involvement.

It has been postulated that dopamine receptor blockage in the hypothalamus may alter heat dissipation.[6] Severe muscle rigidity may also contribute to the hyperthermia. Treatment with anticholinergic agents or benzodiazepam has had limited success. Bromocriptine, a dopamine agonist, has produced dramatic improvement within two hours in a critically ill patient.[7] In our patient, benztropine mesylate did not alter the course of the illness. While the symptoms decreased within 24 hours of the start of carbidopa-levodopa therapy, suggesting a therapeutic result, it was possible that the illness was already improving. The use of a direct-acting muscle relaxant, dantrolene, has been associated with a marked improvement over a 48-hour period.[8–10] Pancuronium has also been successfully used.[11]

William H. Shafer, M.D.
Department of Internal Medicine
The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio 44106

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