Neuroleptic Malignant Syndrome

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Neuroleptic malignant syndrome is a potentially lethal condition of unclear cause seen in as many as 1 percent of patients taking neuroleptic medications.[1] The syndrome was first described in 1959 by Preston[2] and is characterized by hyperthermia, muscular rigidity, mental status changes, and autonomic instability. Widespread use of neuroleptic and other psychotropic medications has made the diagnosis and management of neuroleptic malignant syndrome important for all primary care physicians.

Case Report

A 57-year-old man with an 18-year history of paranoid schizophrenia was successfully managed with trifluoperazine (Stelazine™). The patient came to the office with complaints of increasing stiffness, confusion, and anorexia, which were diagnosed as extrapyramidal side effects of his neuroleptic medication. He was treated sequentially with oral benztropine (Cogentin™), trihexyphenidyl (Artane™), and diphenhydramine (Benadryl™) without success. After 11 days of therapy without improvement, he was admitted to the hospital.

The patient was a thin, well-groomed man who walked with a shuffling gait. A mental status examination revealed mild confusion, but no delusions or hallucinations. His temperature, blood pressure, and pulse and respiration rates were normal. His facies were masked with marked tongue fasciculations. Extremity examination showed bilateral "lead pipe" rigidity and a coarse hand tremor.

On admission a laboratory evaluation of his creatine phosphokinase (CPK) level was 3.98 μkat/L (239 U/L) (normal laboratory value is < 4.48 μkat/L [269 U/L]). The CPK was 100 percent MM fraction. Results of a chest radiograph, complete blood count, electrocardiogram, electrolyte measurement, and thyroid and liver function tests were normal. Magnetic resonance imaging of the brain showed mild atrophic changes with no intracerebral bleeding or mass.

Trifluoperazine was discontinued. The patient was given benztropine mesylate (Cogentin™), amantadine (Symmetrel™), and bromocriptine (Parlodel™) sequentially without relief of rigidity. On the 4th hospital day, he began exhibiting bizarre behavior for which loxapine hydrochloride (Loxitane™), a less-potent neuroleptic, was prescribed. On the 7th hospital day, the patient became markedly more rigid and his oral temperature was 40.1°C (104.2°F). A repeat CPK was 10.92 μkat/L (655 U/L). The diagnosis of neuroleptic malignant syndrome was made, and the patient was transferred to the critical care unit. Findings from a chest radiograph, blood cultures, urinalysis, urine culture, thyroid function tests, and a lumbar puncture were all normal. The patient received intravenous dantrolene sodium (Dantrium™) and benztropine, as well as oral bromocriptine. To avoid the possibility of acute renal failure from myoglobinuria, the patient was provided with vigorous hydration. A cooling blanket helped control hyperthermia. He had several short-lived hypotensive episodes that responded to Trendelenburg positioning and intravenous fluid.

By the 8th hospital day, the patient was afebrile, and his blood pressure was stable. Because of residual stiffness and a rising CPK, oral doses of dantrolene, bromocriptine, and benztropine were maintained. His CPK peaked at 48.46 μkat/L (2907 U/L) on day 9 but fell steadily thereafter. Renal function remained normal. As he continued to improve, he was gradually weaned from his medications. On hospital day 17, the patient was discharged to his home. At that time he was free of any delusions, hallucinations, or confusion and had only minimal rigidity. The benzodiazepine clonazepam (Klonopin™) was prescribed for mild agitation, however, and the dopamine agonist amantadine was continued for his residual rigidity.

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This article is dedicated to the memory of Mark A. Connelly, M.D., who was killed while serving in the Persian Gulf War.

Clinical Presentation

As illustrated above, neuroleptic malignant syndrome is characterized by muscular rigidity, hyperpyrexia, altered mental status, and autonomic instability. Muscular hypertonicity is the most common presenting symptom. It has been described as having a "lead pipe" quality and can be associated with dyskinetic or choreiform movements.[3] The fever of neuroleptic malignant syndrome occurs in conjunction with or shortly after the onset of muscular rigidity; it can be quite dramatic, and temperatures can reach 41°C or higher.[2] The patient's level of consciousness can range from mild confusion to obtundation or coma.[4] Autonomic dysfunction can be manifested by incontinence, diaphoresis, pallor, labile blood pressure, and tachycardia.[5] Less frequent signs of neuroleptic malignant syndrome include seizures, trismus, oculogyric crisis, sialorrhea, retrocollis, the Babinski sign, and opisthotonos.[6]

Although no laboratory test is pathognomonic of neuroleptic malignant syndrome, there are suggestive findings. As a result of intense muscular rigidity, serum CPK is often elevated and can be as high as 1250.25 μkat/L (75,000 U/L).[7] Leukocytosis, with a cell count in the range of $15–30 \times 10^9$/L (15,000–30,000/mm^3), with or without a left shift, might also be present.[4] Electrolytes can reflect dehydration. Other abnormalities can include elevated liver function tests.[5] An electroencephalogram can show diffuse slowing or be normal.[4] Cerebrospinal fluid analysis is normal, as is central nervous system structure when visualized by computed tomography or at postmortem autopsy.[4]

The patient with neuroleptic malignant syndrome must be carefully observed for signs of complications. Decreased chest wall compliance caused by muscle rigidity can result in aspiration pneumonia or respiratory failure.[3] Intense muscle contraction can lead to myonecrosis, myoglobinuria, and acute renal failure.[8] Other complications include disseminated intravascular coagulation,[9] *Escherichia coli* fascitis, cardiac dysrhythmias, and thromboembolism.[5] The estimated mortality for neuroleptic malignant syndrome ranges from 20 to 30 percent.[4]

Cause and Pathophysiology

Neuroleptic malignant syndrome is an idiosyncratic reaction that can occur in either sex, at any age, and in both medical and psychiatric patients. There is a 2:1 predominance of men to women.[10] Although most often associated with neuroleptic drugs, this syndrome also has been reported after treatment with tricyclic antidepressants and monoamine oxidase inhibitors, as well as after the withdrawal of dopaminergic antiparkinsonian medicines, such as amantadine and levodopa.[5,10] Of the neuroleptic drugs, the depot formulations (e.g., fluphenazine decanoate and haloperidol decanoate) and those with the highest antidopaminergic potency (e.g., droperidol, haloperidol, trifluoperazine, and thiothixene) are most likely to induce an episode of neuroleptic malignant syndrome.[6] Other predisposing factors include dehydration, electrolyte imbalances, exhaustion, organic brain syndrome,[5] and hypothyroidism.[11]

The exact pathophysiology of neuroleptic malignant syndrome is unknown. It has been theorized, however, that its clinical features are due to either a disruption of certain central nervous system pathways or to a peripheral induction of intense striated muscle contraction.

The first theory proposes that central dopaminergic blockade leads to the symptoms seen in neuroleptic malignant syndrome. More specifically, the hyperthermia is thought to be precipitated by hypothalamic pathway blockade, while the muscular rigidity is believed to result from the blockage of nigrostriatal pathways. This theory is supported by the success of such central dopamine agonists as bromocriptine in treating neuroleptic malignant syndrome.[12]

The second theory relies upon the similarity of neuroleptic malignant syndrome to malignant hyperthermia, an inherited autosomal dominant trait. Malignant hyperthermia is characterized by muscular rigidity and hyperpyrexia triggered by inhaled anesthetics, most commonly halothane.[13] In susceptible individuals, these agents cause an increase of calcium permeability of skeletal muscle sarcoplasmic reticulum resulting in unregulated actin and myosin cross-bridge cycling and tetani. If unchecked, this process results in increased heat production, generalized cellular destruction, and eventually death. The response of both malignant hyperthermia and neuroleptic malignant syndrome to dantrolene therapy, which decreases sarcoplasmic reticulum calcium per-

meability, is suggestive of a common cause for both syndromes.[14]

Unlike malignant hyperthermia, however, there appears to be no genetic transmission of neuroleptic malignant syndrome. Also, whereas curare or pancuronium will cause a flaccid paralysis in those with neuroleptic malignant syndrome, they have no effect on patients with malignant hyperthermia.[15] Obviously, there is much that remains to be elucidated concerning the pathogenesis of neuroleptic malignant syndrome.

Differential Diagnosis

Neuroleptic malignant syndrome is largely a clinical diagnosis. The patient's psychiatric and pharmacologic history, combined with a good review of systems and physical examination, should lead the clinician quickly to consider neuroleptic malignant syndrome. The dramatic symptoms of neuroleptic malignant syndrome, however, usually prompt consideration of other significant diagnostic possibilities (Table 1).

One must consider central nervous system infection, given the patient's hyperthermia and mental status changes. Meningitis and encephalitis are possibilities, thus a white cell count and lumbar puncture with cerebrospinal fluid examination are indicated. The cerebrospinal fluid is always normal in neuroleptic malignant syndrome.[5] Careful neurologic examination and perhaps neurology consultation will augment the history to help exclude movement disorders, such as severe Parkinson disease or Huntington chorea. Other central nervous system insults, such as trauma, tumor, hemorrhage, or infarction, can lead to a symptom complex similar to that seen in neuroleptic malignant syndrome. Computed tomographic or magnetic resonance imaging will help identify these intracerebral possibilities.

Table 1. Differential Diagnosis of Neuroleptic Malignant Syndrome.

Central nervous system infection
Meningitis
Encephalitis
Movement disorder with fever from another source
Parkinson disease
Chorea
Cerebrovascular accident
Trauma
Tumor
Hemorrhage
Infarction
Heat stroke
Malignant hyperthermia
Thyroid storm
Lethal catatonia

Heatstroke is a possibility, if the patient taking a neuroleptic medication is exposed to high ambient temperatures and humidity or is additionally predisposed to heat injury in some way. The neuroleptic medications do increase risk for temperature regulation difficulties. One may well see elevated CPK in heatstroke victims, but muscle rigidity is less common.[5]

As noted above, malignant hyperthermia must be considered when there has been any recent history of exposure to inhalation anesthetics. Also, as previously mentioned, a therapeutic trial of pancuronium or curare can be helpful in differentiating between neuroleptic malignant syndrome and malignant hyperthermia. This is not without risk, however, and requires immediately available respiratory support.[16]

Thyroid storm should also be included in the differential diagnosis, especially in patients who have a history of thyroid disease. Serum triiodothyronine (T_3), thyroxine (T_4), T_3 resin uptake, and free T_4 index should be measured early in the evaluation of these patients.

Lethal catatonia was first described in 1934. Its cause is unclear, but it seems related to a state of prolonged extreme agitation, usually mania, leading to fever, dehydration, electrolyte imbalances, and disruption in calcium metabolism. Autonomic dysfunction is usually not described. This potentially fatal complication can be seen in psychiatric patients who do or do not take neuroleptic medications.[15]

Treatment

After a careful differential diagnosis is rapidly entertained and evaluated, treatment for neuroleptic malignant syndrome must begin immediately (Table 2). Discontinuation of the causative agent should be followed quickly by transfer to an intensive care setting for one-on-one nursing. Aggressive supportive measures are aimed at lowering body temperature, as well as maintaining blood pressure, tissue perfusion, and renal function. Serum electrolytes, blood urea nitrogen, creatinine, and CPK levels should be measured frequently.

Simultaneously, specific pharmacologic treatment should be initiated. Dantrolene is a direct-

Table 2. Treatment of Neuroleptic Malignant Syndrome.

Remove inciting agent
Aggressive supportive care — transfer to intensive care unit
Lower body temperature
Support blood pressure
Insure renal perfusion
Specific pharmacologic therapy
Dantrolene sodium
Dopamine agonists (bromocriptine)
Anticholinergics (trihexyphenidyl, benztropine)

acting muscle relaxant that, by blocking leakage of calcium from the sarcoplasmic reticulum, decreases peripheral muscular rigidity. This action lowers fever and decreases rhabdomyolysis.[5,8] Initially, the dosage is 2 to 10 mg/kg/d intravenously in four divided doses. After stabilization, the oral maintenance dosage ranges from 50 to 200 mg/d in four divided doses. Upon institution of the dantrolene therapy, one should see a decrease in muscular rigidity and a falling CPK level.

Another important pharmacologic agent is the central dopamine agonist bromocriptine. Bromocriptine is a direct postsynaptic dopamine receptor agonist that works to reverse central dopaminergic blockade.[4,5] It is given as 2.5 to 10 mg orally three times a day. A good starting dose during a crisis is 5 mg three times daily. While the mainstay of dopamine agonist therapy remains bromocriptine,[17] such presynaptic agents as amantadine have been tried with limited success. The initial dose for amantadine is 100 mg orally twice daily. Dialysis is not effective because most neuroleptics are significantly protein bound and therefore not dialyzable. Prior to the demonstrated efficacy of dantrolene and bromocriptine, the pharmacologic treatment of choice was the anticholinergic agents. Trihexyphenidyl (Artane™)[10,18] and benztropine (Cogentin™)[6] have been used most commonly in an attempt to reverse the severe anticholinergic and extrapyramidal effects of the offending agent.

As with all critical care patients, it is important to keep in close communication with family members. Neuroleptic malignant syndrome is usually dramatic in its evolution and treatment, and a well-informed family will serve as a valuable ally in the care of the patient.

Prognosis

If the patient survives, recovery occurs over days to weeks. Low-dose pharmacologic therapy is continued as needed. Recovery can proceed more slowly in schizophrenic patients than in other medical patients with neuroleptic malignant syndrome.[19] Unless absolutely necessary, neuroleptic agents should not be restarted. Recurrence of neuroleptic malignant syndrome after reinstitution of antipsychotic medications is well documented. Even the new antipsychotic clozapine (Clozaril™) has been implicated in causing neuroleptic malignant syndrome.[20,21] Certainly, psychiatric consultation would be in order before reinstituting any antipsychotic medication.

Summary

Neuroleptic malignant syndrome is a relatively uncommon life-threatening disorder. The widespread use of the neuroleptic and psychotropic medications, however, makes it important for the primary care physician to understand the clinical presentation, differential diagnosis, and management of neuroleptic malignant syndrome. Early recognition should be possible. Rapid diagnosis followed by aggressive supportive care and specific pharmacologic therapy can be life saving.

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