Neuroleptic malignant syndrome from central nervous system insult: 4 cases and a novel treatment strategy

Clinical article

Scott D. Wait, M.D., Francisco A. Ponce, M.D., Brendan D. Killory, M.D., Donna Wallace, P.N.P., and Harold L. Rekate, M.D.

Divisions of Neurological Surgery and Pediatric Neurosciences, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona

Neuroleptic malignant syndrome (NMS) is a potentially life-threatening entity characterized by hyperthermia, autonomic deregulation, decreased mental status, increased muscle tone, and, frequently, by renal failure due to rhabdomyolysis. Classically, it follows administration of antipsychotic medication.

The authors report on 4 patients (2 children and 2 adults) in whom NMS was diagnosed after a CNS insult. No patient was receiving antipsychotic medication. The patients' hospital and clinic charts, radiographic data, and follow-up telephone conversations were reviewed retrospectively.

All 4 patients met diagnostic criteria for NMS. Three patients presented with shunt failure, and 1 patient had undergone a functional hemispherectomy 2 days earlier. One patient with shunt failure received the diagnosis retrospectively. An endoscopic third ventriculostomy alleviated his shunt failure and he remains free of NMS. The other 2 patients underwent treatment for shunt failure, but NMS remained. These 2 patients and the one who had undergone hemispherectomy underwent a trial of intrathecal baclofen, and the NMS resolved. Subsequently, an intrathecal baclofen infusion device was placed in all 3 patients, and the NMS resolved. The 2 patients in shunt failure had a lumbar intrathecal baclofen infusion device. The patient who had undergone hemispherectomy had an intracranial baclofen catheter.

Neuroleptic malignant syndrome is a rare, life-threatening disorder that can occur without the administration of neuroleptic medications. Alleviation of any CNS insult is the first order of treatment. Some patients with persistent symptoms of NMS may benefit from intrathecal delivery of baclofen. (DOI: 10.3171/2009.4.PEDS08444)

Key Words • intrathecal baclofen infusion device • epilepsy • hydrocephalus • neuroleptic malignant syndrome

Abbreviations used in this paper: ETV = endoscopic third ventriculostomy; ICP = intracranial pressure; NMS = neuroleptic malignant syndrome; VP = ventriculoperitoneal.

according to Levenson's system for diagnosing NMS, major criteria consist of fever, rigidity, and elevated creatinine and phosphokinase levels. Minor criteria consist of tachycardia, abnormal arterial pressure, altered level of consciousness, diaphoresis, and leukocytosis. To make a diagnosis of NMS, the patient's condition must include all 3 major criteria or 2 major and 4 minor criteria. We report on 4 patients in whom NMS was diagnosed based on these criteria. None of the patients had received neuroleptic medications. All 4 had suffered an insult to the CNS: 3 had acute hydrocephalus, and 1 had undergone hemispherectomy for epilepsy. Neuroleptic malignant syndrome in conjunction with CNS derangement has been described. However, this condition has not been reported in patients after shunt malfunction or resection. Because this condition is usually misdiagnosed
as either an infectious complication or hypothalamic dysregulation, neurosurgeons should be aware of the potential for it to develop in their patients. The problem resolved in 1 of our patients after ETV. Three patients required intrathecal baclofen to abate their NMS. We describe the clinical presentation, treatment rationale, treatment, and postoperative course of these patients and outline a novel strategy for administering intrathecal baclofen to patients suffering from intractable NMS.

Case Series

We performed a retrospective chart review of all patients treated at the Barrow Neurological Institute of St. Joseph’s Hospital and Medical Center for NMS temporally related to CNS insult from 1992 until the present. We evaluated hospital and clinic charts, radiographic data, operative reports, and telephone conversations with the patients and/or their parents. Surgeries were performed under standard sterile conditions. No new method was used to implant the intrathecal baclofen infusion device. The intracranial baclofen catheters were tunneled and inserted in a manner identical to standard VP shunt treatment.

Case 1

This 27-year-old man with neurofibromatosis Type 1 and a tectal glioma had undergone multiple shunt revisions. He presented with abdominal pain, and his VP shunt was converted to a ventriculoatrial shunt. Afterward he failed to awaken, and he demonstrated decerebrate posturing. A CT scan revealed that he had ventriculomegaly. The shunt was removed at the bedside, and a ventriculostomy catheter was placed. Cerebrospinal fluid was drained at a level of −15 cm to decrease the size of the ventricles. Despite his ventriculomegaly and negative ICP, the patient was comatose. His blood pressure was 200/140 mm Hg, his temperature was 105°F, and his pulse was 180 bpm. Laboratory values revealed decreased renal function (creatinine phosphokinase (254 U/L), renal failure (creatinine 1.9 mg/dl), cardiovascular lability, and respiratory failure. He was treated with deep propofol sedation, which helped improve his neurological status and NMS but did not cure it. Lightening the propofol sedation prompted a return of his symptoms. A tracheostomy was performed, and a feeding tube was placed. After 27 days of this scenario, the lumbar CSF cistern was accessed via lumbar catheter, and instillation of baclofen at 100 μg/day was started and increased to 250 μg/day. The patient’s neurological examination, laboratory values, and vital signs returned to normal. A lumbar intrathecal baclofen infusion device was implanted and set to deliver 250 μg/day. He was discharged to rehabilitation 6 days later. He was neurologically intact with a short-term memory deficit. On 2 occasions the patient returned to the hospital in florid NMS after attempts to ween him from the intrathecal dose. At 5 years he is neurologically intact with only mild cognitive deficits.

Case 2

This 40-year-old man suffered a closed head injury. A ventriculostomy catheter was placed to monitor ICP and to drain CSF. When the ventriculostomy was closed, he developed ventriculomegaly and a VP shunt was placed. Subsequently, a subdural hematoma developed, which was evacuated via a craniotomy. He ultimately required a combination subdural-to-peritoneal shunt and VP shunt with both catheters connected proximal to the programmable valve. During attempts at weening, resistance to flow was increased incrementally. Two days later he presented to the hospital with ventriculomegaly, decreased mental status, rigidity, fever, tachycardia, elevated creatine kinase (12,852 U/L), renal failure (creatinine 1.9 mg/dl), cardiovascular lability, and respiratory failure. He was treated with deep propofol sedation, which helped improve his neurological status and NMS but did not cure it. Lightening the propofol sedation prompted a return of his symptoms. A tracheostomy was performed, and a feeding tube was placed. After 27 days of this scenario, the lumbar CSF cistern was accessed via lumbar catheter, and instillation of baclofen at 100 μg/day was started and increased to 250 μg/day. The patient’s neurological examination, laboratory values, and vital signs returned to normal. A lumbar intrathecal baclofen infusion device was implanted and set to deliver 250 μg/day. He was discharged to rehabilitation 6 days later. He was neurologically intact with a short-term memory deficit. On 2 occasions the patient returned to the hospital in florid NMS after attempts to ween him from the intrathecal dose. At 5 years he is neurologically intact with only mild cognitive deficits.

Case 3

This 19-year-old woman underwent VP shunt placement at another institution for presumed pseudotumor cerebri. She presented in shunt failure with ventriculomegaly (Fig. 1), decreased level of consciousness, fever, rigidity, tachycardia, elevated creatine kinase (254 U/L), and leukocytosis. Emergency shunt revision resolved her ventriculomegaly, but her NMS remained. Electroconvulsive therapy failed to resolve her NMS. This situation persisted for 16 days. Subsequently, a lumbar CSF drainage catheter was placed, and intrathecal baclofen was started at 200 μg/day. Her level of consciousness improved significantly. Her laboratory and hemodynamic parameters returned to normal, and her tone improved. A lumbar intrathecal baclofen infusion device was implanted, and the patient was discharged to rehabilitation with an infusion.
Intracranial baclofen for neuroleptic malignant syndrome

Case 4

This 45-month-old child presented to our institution for evaluation of complex partial seizures. He was a twin born at 36 weeks. The demise of his twin at 14 weeks' gestation resulted in a hypercoagulable state with multiple intracranial emboli. Most of the patient’s right hemisphere was absent or dysplastic (Fig. 2). Evaluation in the epilepsy monitoring unit revealed the existing right hemisphere to be the source of his seizures, and he was scheduled for a right hemispherectomy. Surgery was performed in a standard fashion, sparing the basal ganglia.

The boy’s postoperative course was uncomplicated until postoperative Day 2 when he developed high-grade fever, a decrease in neurological status, extreme rigidity, tachycardia, blood pressure lability, increased white blood cell count, and elevated creatine kinase levels (963 U/L). Findings on routine CT scanning were unremarkable. Consequently, a ventriculostomy catheter was placed in the empty hemisphere. The patient’s ICP was normal. He underwent CSF drainage, but his symptoms failed to resolve. Escalation of his oral baclofen dose helped but did not resolve his symptoms, and he suffered respiratory depression from the baclofen. Intrathecal baclofen was started on postoperative Day 14 at 50 µg/day and titrated to 150 µg/day over 5 days. The NMS resolved and he returned to his neurological baseline. Attempts to ween him from the intrathecal baclofen resulted in the return of his symptoms. We proposed insertion of a permanent indwelling intracranial catheter attached to an intrathecal baclofen infusion device (Fig. 3). This off-label use was described to his parents, and they asked us to proceed. The surgery was uneventful. Since then his dosage has been increased to 225 µg/day, and the NMS has not recurred. At 18 months after pump implantation, he is seizure free and at his neurological baseline.

Discussion

Pathophysiology

Neuroleptic malignant syndrome is a potentially life-threatening disorder most often attributed to the administration of neuroleptic medication. Inhibition of normal CNS dopaminergic pathways is the cause.4,11 Central hypothalamic inhibition of dopamine is thought to be responsible for hyperthermia and the autonomic manifestations such as arrhythmias, hypo- or hypertension, and tachypnea. Striatal dopaminergic inhibition is thought to be responsible for the rigidity and tremor. A direct effect on peripheral muscles may play an additive role.3

Related Diagnoses

There are several related diagnoses, including malignant hyperthermia, acute lethal catatonia, neuroleptic-induced heat stroke, and serotonin syndrome.3 Malignant hyperthermia is differentiated by history. It is usually induced by halogenated inhalational anesthetics or depolarizing muscle relaxants such as succinyl choline. Masseter spasm on induction with succinyl choline, resistant hypercarbia, acidosis, and an increase in temperature are the hallmarks of this syndrome. Treatment includes with-
drawing the offending agent and providing cardiorespiratory support.\textsuperscript{3}

Acute lethal catatonia involves akinesia, hyperthermia, and rigidity. Before the onset of the syndrome, patients may have stereotypic movements, choreiform movements, and posturing. Weeks of behavioral changes may precede the appearance of motor symptoms. Patients often receive antipsychotics after the onset of their movements, rather than antipsychotic administration precipitating the syndrome as is most often the case with NMS.\textsuperscript{3}

Neuroleptic-induced heat stroke most often occurs in elderly patients on antipsychotic medications who were recently exposed to exercise or heat. It is postulated to stem from central dopaminergic blockade and peripheral anticholinergic effect leading to decreased sweating and impaired heat dissipation. Features include hyperthermia, altered consciousness, pallor, and sometimes seizures. Seizures are seldom associated with NMS. Rigidity, sweating, and involuntary movements are absent. Treatment consists of cooling and administration of fluids while temperature is monitored closely.\textsuperscript{3}

Serotonin syndrome occurs after an overdose of selective serotonin reuptake inhibitors or their use in combination with monoamine oxidase inhibitors, tricyclic antidepressants, or meperidine. The following 4 symptoms combine to define serotonin syndrome: changes in mental status, neuromuscular symptoms, autonomic dysfunction, and gastrointestinal dysfunction.\textsuperscript{14} It is distinguished from NMS by the presence of nausea, vomiting, and diarrhea, features that are atypical of NMS. Shivering, ataxia, myoclonus, hyperreflexia, and ankle clonus also may be present in serotonin syndrome but seldom in NMS.\textsuperscript{3}

Treatment of NMS

Withdrawal of any offending agent is the first line of treatment. In our cases, no neuroleptic agent had been administered. Pharmacological treatment in an intensive care setting, with bromocriptine and dantrolene, is the next line of treatment. These medications are thought to help shorten the course of NMS, but some authors disagree.\textsuperscript{13} In refractory cases or when it is difficult to distinguish NMS from lethal catatonia, electroconvulsive therapy may prove useful.\textsuperscript{19,20} This modality is thought to work by restoring dopamine receptor sensitivity, but it is not well understood.\textsuperscript{6,22} The patient in Case 3 underwent electroconvulsive therapy, but further treatment was required to resolve her syndrome.

Current Case Material

In our 4 cases we suspected that a CNS insult (hydrocephalus in 3 and hemispheric resection in 1) that interrupted 1 or more of the 3 major central dopaminergic pathways was the cause of NMS. In Cases 1, 2, and 3, rapid third ventricular dilation, hypothalamic distension, and disruption of the hypothalamic-pituitary system were probably responsible. In Case 4 extensive cortical resection and interruption of the mesolimbic/cortical system was the likely cause. We have no direct evidence to support this assertion, but it seems to be the most logical explanation given these patients’ lack of exposure to neuroleptics, the temporal relationship between CNS insult and the development of NMS, and the anatomical correlate with each respective pathology. In the patient in Case 1 the NMS resolved with correction of his hydrocephalus and medical treatment, indicating that damage to the dopaminergic pathway might have been transitory. That NMS failed to resolve in Cases 2 and 3 after correction of the patients’ hydrocephalus and medical treatment indicates that dopaminergic pathway damage can also be permanent or slow to recover. The patient in Case 4 underwent hemispherectomy and was unable to have his CNS insult “corrected.”

The patient in Case 1 underwent ETV, and both his hydrocephalus and NMS resolved. Now 13 years after his ETV, he has shown no signs of NMS. Should his ETV become occluded and cause hydrocephalus and medically intractable NMS, we would consider intrathecal baclofen for his treatment.

Patients who experience abrupt withdrawal of intrathecal baclofen often develop high fever, profound muscular rigidity, altered mental status, cardiovascular lability, and rhabdomyolysis, a syndrome virtually indistinguishable from NMS.\textsuperscript{7,9,10,18,21} This similarity to NMS prompted us to consider intrathecal baclofen delivery in the patients in Cases 2, 3, and 4 who had medically intractable NMS. Baclofen is an agonist of γ-aminobutyric acid type B. Baclofen is known to exert its effects in the spinal cord by binding to presynaptic γ-aminobutyric acid type B receptors causing inhibition of the α–motor neuron and relaxation of spasticity.\textsuperscript{9} This mechanism may explain its role in some aspects of NMS reversal. Resolution of hypertonicity, rhabdomyolysis, fever, and renal failure can all be explained by relaxing muscle tone. The exact mechanism of action in the brain is thought to be via inhibition of widespread areas of the brain, including the cerebral cortex, thalamus, cerebellum, basal ganglia, and spinal cord.\textsuperscript{21} However, the mechanism by which baclofen penetrates and affects the brain is unknown.\textsuperscript{13}

Although not previously reported as treatment for NMS, we placed lumbar drainage catheters in Cases 2 and 3 and instilled test doses of intrathecal baclofen. The patients’ clinical improvement was significant and durable. Accordingly, these patients had a standard intrathecal baclofen infusion device placed with lumbar catheters. The patient in Case 3 has undergone 2 attempts at weening from the baclofen, but his NMS symptoms returned each time. No further attempts at weening will be made. The patient in Case 2 has undergone no weening trials.

The patient in Case 4 had medically intractable NMS. Because of his confusing clinical picture, we placed a ventriculostomy catheter into the right hemispheric resection cavity to measure pressure (normal) and to control drainage of CSF. When his condition failed to improve, we recognized that the intracranial catheter afforded a way to instill baclofen directly into the intracranial space. Previous reports have indicated that intracranial baclofen instillation was safe in 2 patients with dystonia, and no radiographic or histological evidence of CNS damage was evident in beagles given intraventricular baclofen.\textsuperscript{1,2} The
Intracranial baclofen for neuroleptic malignant syndrome

patient in Case 4 improved significantly with 72 hours of intracranial baclofen administration. He never showed signs of sedation or respiratory depression from CNS baclofen, although he did from oral baclofen.

Conclusions

Neuroleptic malignant syndrome can result from CNS insult. Rapid identification of this syndrome and correction of the primary CNS pathology, when possible, is the first line of treatment. Patients resistant to correction and maximum medical therapy may benefit from installation of intrathecal baclofen. Select patients may see profound improvement, although the time course is variable. Intracranial and intraspinal instillation of baclofen can be a safe and effective treatment for this difficult problem. Further work to elucidate the pathophysiology of disease and method of action of intrathecal baclofen is warranted.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References


Manuscript submitted December 4, 2008.
Accepted April 16, 2009.

Address correspondence to: Harold L. Rekate, M.D., c/o Neuroscience Publications Office, St. Joseph’s Hospital and Medical Center, 350 West Thomas Road, Phoenix, Arizona 85013. email: neuropub@chw.edu.