Behavioral Manifestations of Central Pontine Myelinolysis

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A young woman with a clinical history and magnetic resonance imaging scan consistent with central pontine myelinolysis came to medical attention because of prominent behavioral symptoms. Marked clinical recovery occurred despite persistent radiologic abnormalities. Rapid correction of hyponatremia was probably related to the development of the central pontine myelinolysis. A normal computed tomographic scan and the absence of brain-stem signs delayed accurate diagnosis.

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Central pontine myelinolysis (CPM) was first described by Adams et al in 1959. Early descriptions emphasized its grave prognosis. More recent reports have documented survival and recovery. Ventral pontine involvement with subacute onset of cerebellar, cranial nerve, and pyramidal tract dysfunction is the typical presentation.

We describe a patient in whom reversible behavioral abnormalities constituted the major manifestation of CPM. One purpose of this article is to alert physicians to the possible behavioral presentation of CPM. Another is to emphasize the relationship between rapid correction of hyponatremia and CPM. We also forward some thoughts on the pathophysiology of these behavioral changes.

REPORT OF A CASE

A 29-year-old right-handed professional woman was in excellent health until her return from Mexico. She developed intractable nausea, anorexia, and diarrhea for one week, leading to a 2.2-kg (5-lb) weight loss.

Results of a clinical examination at that time were normal, except for orthostatic hypotension. Laboratory test results disclosed the following values: serum sodium, 114 mEq/L (114 mmol/L); potassium, 1.9 mEq/L (1.9 mmol/L); arterial blood gases demonstrated respiratory alkalosis; her alanine aminotransferase level was elevated to 128 U/L; and aspartate aminotransferase, to 115 IU/L. Campylobacter was grown from her stools. There was no history of major psychiatric disease in the patient or her family.

She received 2 L of normal saline with potassium supplementation. Seventeen hours later, her sodium level was 133 mEq/L (133 mmol/L), and her potassium level was 4.2 mEq/L (4.2 mmol/L). She recov-

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ered uneventfully and was discharged after two days.

Six days after discharge, while on duty, her colleagues noted inappropriate, confused, and restless behavior. Neurologic examination disclosed an inattentive, agitated woman with pressured, tangential speech, mild dysarthria, word-finding difficulties, and right-hand clumsiness. Judgment and insight were markedly impaired. She kept circulating throughout the hospital despite admonishment to remain in her room, denied the importance of her illness, groomed herself publicly in the hallways, spoke of her difficulties to strangers, and inappropriately attempted to resume her professional activities. Other than occasional paraphasic errors, no cognitive deficits were apparent.

Results of laboratory tests, including a complete blood cell count, electrolytes, thyroid functions, vitamin B12 and folate levels, toxic screens, antinuclear antibody, hepatitis B surface antigen (HBsAg), and echocardiogram were unremarkable, as was a contrasted computed tomographic (CT) scan of the head. Her erythrocyte sedimentation rate was elevated to 37 mm/h. Cerebrospinal fluid analysis, including IgG and oligoclonal bands, was normal. Bilateral carotid angiogram and visual, auditory, median, and tibial somatosensory evoked potentials were normal. Electroencephalography (EEG) showed left anterior sylvian to midtemporal delta slowing and occasional bitheral generalized sharp waves. Magnetic resonance imaging (MRI) scanning using steady-state free procession and spin-echo sequences with sagittal and axial images demonstrated a triangular area of increased signal intensity in the midportion of the pons without mass effect (Fig 1).

The patient's behavior, speech, and dexterity returned to normal over a period of two weeks. In four weeks, she returned to her occupation full-time without difficulty. An EEG performed three months after discharge demonstrated high-voltage alpha bursts over the left anterior and midtemporal region, with brief paroxysmal generalized bifrontal theta. Her erythrocyte sedimentation rate returned to normal, electrolytes remained stable, and a repeat MRI scan performed 2½ months after onset showed no change in the appearance of the brain-stem lesion. Twelve months after onset, she continues to do well.

COMMENT

Patients who subsequently develop CPM characteristically arrive at the hospital in a debilitated state with a low serum sodium level. There are many reports of intractable nausea, vomiting, and diarrhea prior to admission. Though frequently associated with Wernicke's encephalopathy and chronic alcoholism, CPM may occur in the context of other conditions such as pneumonia, neoplasms, malnutrition, ataxia, weight loss, gastrointestinal bleeding, Wilson's disease, and renal transplantation. The peak age of incidence is the fourth through seventh decades; however, CPM has been documented in children as well. A low sodium level with rapid correction (or overcorrection) is a common feature, and may constitute an important factor in the cause of the myelinolysis. A positive correlation between the severity of the sodium deficits, the rate of its correction, and the size of the lesion has been suggested. The rapid correction of electrolytes and especially serum sodium in these patients is thought to lead first to improvement, and then, in three to ten days, to the pontine myelinolysis with associated cerebellar ataxia, cranial nerve dysfunction, and quadriparesis with respiratory difficulties.

Emotional lability, especially crying, has been reported in CPM and thought to be secondary to corticobulbar lesions. Confusion and disorientation have been noted in some patients, and may precede other signs or symptoms. However, the cause of these symptoms is unclear, given the associated diseases that can independently lead to a metabolic encephalopathy. The behavioral changes described in CPM are almost always overshadowed by more prominent brain-stem signs. The maximal neurologic deficit usually emerges one to three weeks later, and, in severe cases, intercurrent illness causes death two to four weeks after onset. In other instances, improvement and complete recovery have been reported.

Cerebrospinal fluid analysis in CPM is usually normal. Brain-stem auditory evoked potentials may or may not demonstrate prolongation of wave I through V latencies. The CT scan may demonstrate a nonenhancing, hypodense ventral-pontine lesion, but normal CT scans have also been reported. The CT abnormality may last longer than clinical symptoms. In one patient who completely recovered after six months, only partial CT resolution was apparent after 12 months, with complete CT resolution shown 22 months after onset. The EEG is usually normal or nonspecific. Magnetic resonance imaging scans have been reported to show an abnormal density signal in the ventral pons without mass effect. Repeated MRI scans performed 15 weeks to eight months later may or may not demonstrate interval changes, despite clinical improvement. A specific antemortem test for the diagnosis of CPM is currently unavailable.

In our patient, the diagnosis of CPM is suggested mostly by the MRI scan abnormality and the rapid correction
of hyponatremia eight days prior to the onset of symptoms. Albeit mild, the right-handed clumsiness, the dysarthria, and the rate of clinical resolution are consistent with this diagnosis. The marked behavioral abnormalities in the absence of prominent brain-stem signs and the setting of a young person in good underlying health are the unusual features. The EEG focality and language impairments are atypical in that they indicate a lesion in the left hemisphere, but they could be associated with extra pontine myelinolysis that has been reported in CPM.9

PATHOANATOMIC STUDIES

Central pontine myelinolysis is a unique clinical pathologic entity, which involves median pontine structures and usually spreads in a centrifugal, symmetric fashion. It may involve the corticospinal, corticobulbar, and pontocerebellar tracts, cranial nerves, and other ventral pontine structures. Extensive involvement of the midbrain, pontine tegmentum, paramedian reticular area, sym pathetic fibers, and sensory pathways may occur. Approximately 10% of cases have associated extra pontine lesions in the spinal cord, medulla, mesencephalic tegmentum, basal ganglia, cerebellum, internal capsules and thalamus, cerebral peduncles, optic radiations, lateral geniculate bodies, hemispheric white matter, and cerebral cortex. Incomplete demyelination and edema is seen with preservation of nerve cells, axis cylinders, and blood vessels. There are no signs of inflammation. Central pontine myelinolysis as verified by postmortem examination may not be clinically obvious. Of the four cases originally reported by Adams et al, two manifested no clinical symptoms. The small size of their lesions was the suggested explanation. Norenberg et al and Wright et al also reported CPM at postmortem examination, which may not have been clinically apparent.9,10

The exact pathophysiology of our patient's altered behavior remains obscure. Since the onset occurred eight days after correction of her electrolyte abnormalities, a metabolic derangement is unlikely. Instead, it is more plausible that these behavioral alterations were caused by the CPM. The location of the MRI abnormality suggests that the lesion may have interfered with the ascending projections of the raphe nuclei, pontomesencephalic reticular formation, and perhaps even those of the nucleus locus coerules. This would interfere with the cortical and thalamic supply of serotonin, acetylcholine, and noradrenaline, respectively. Considerable evidence indicates that alterations in these neurotransmitter pathways play a role in the modulation of mood and arousal.11

Behavioral abnormalities with other pontine lesions have been reported. In pediatric pontine tumors, profound mental status changes may precede other signs and symptoms.22 These behavioral changes may range from restlessness, irritability, aggression, and rage, to apathy, lethargy, disorientation, and confusion.

Animal experiments suggest that hyponatremia rapidly corrected by hypertonic saline can induce demyelination, whereas hyponatremia alone or its slow correction does not. Current indications are to reverse hyponatremia to prevent seizures and encephalopathy, but to do so slowly. If the serum sodium level is below 105 mEq/L (105 mmol/L), initial correction at 2 mEq/L/h (2 mmol/L/h) is recommended for the first 20 mEq/L (20 mmol/L). The serum sodium level should then be allowed to drift to normal range. If the serum sodium level is 105 mEq/L (105 mmol/L) or greater, it can be corrected at the same rate to a level of 125 to 130 mEq/L (125 to 130 mmol/L). Serum sodium levels above 120 mEq/L (120 mmol/L) usually do not require immediate correction. Adherence to these guidelines could reduce the incidence of CPM.

This patient indicates that CPM should be included in the differential diagnosis of acute behavioral changes, especially if rapid correction of hyponatremia has occurred in the recent past. In fact, CPM may occur more frequently than clinically suspected, and MRI scanning may be essential for accurate diagnosis.

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