Central Pontine Myelinolysis: Case Series and Review

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ABSTRACT

Objective: To review central pontine myelinolysis (CPM) and osmotic demyelination syndrome (ODS) and describe the clinical features, etiologic factors, and clinical outcomes of 6 patients diagnosed with CPM or ODS.

Study Design: A retrospective case series.

Methods: Medical records of patients diagnosed with CPM or ODS at Marshfield Clinic/St. Joseph's Hospital from 1986 to 2003 were reviewed. Chart abstraction was completed with a standardized data abstraction form.

Results: Six patients were identified, ranging in age from 31-73 years (mean age = 51.5 years). Clinical presentations were nonspecific. Common symptoms included lethargy and dysarthria. Five of the 6 patients had chronic alcoholism. All had improvements in their clinical conditions upon hospital discharge.

Conclusions: CPM and ODS are rare demyelinating diseases of the pons and extrapontine sites. Prompt diagnosis and management of associated complications are essential for favorable clinical outcomes.

INTRODUCTION

Adams and colleagues initially described central pontine myelinolysis (CPM) as a clinical entity in 1959.1 They described the disease in 4 patients, all of whom had associated chronic alcoholism and/or malnutrition. Since the initial description by Adams et al, other case reports, case series, and literature reviews have been published describing this clinical condition.

The etiology and pathogenesis of CPM has not been clearly defined and has been reported to occur in the presence of severe underlying illnesses. Most cases have been associated with a history of chronic alcohol abuse and electrolyte disturbances. Clinical manifestations are variable and depend on the region(s) of the brain involved. The typical lesion of CPM is a symmetrical, butterfly-shaped area of demyelination within the central pons. The histological picture shows symmetrical demyelination with intact neurons. Extrapontine sites such as the internal capsule, basal ganglia, cerebellum, and cerebrum can also be affected.1,2 When the pathologic process also involves extrapontine sites, the term osmotic demyelination syndrome (ODS) is used. Cardinal symptoms are generally nonspecific and include a disturbed level of consciousness, pseudobulbar symptoms, and gait abnormalities.

Few single institution case series have been reported in the literature. We report our experience with CPM, describing the clinical features and outcomes in this population.

METHODS

We retrospectively reviewed the medical records of 6 cases of CPM or ODS evaluated at Marshfield Clinic/St. Joseph's Hospital from 1986 to 2003. The clinical presentation, etiologic factors, physical findings, and clinical course were described for each patient. The diagnostic files of the Marshfield Clinic database were electronically interrogated using the ICD-9 diagnostic code 341.8 (other demyelinating diseases of the central nervous system). Cases were confirmed by chart review. Chart abstraction was completed using a standardized data abstraction form. The Institutional Review Board approved the study.

RESULTS

Six patients were identified, ranging in age from 31-73 years with a mean age of 51.5 years. The majority of patients were Caucasian males with demyelination within
the central pons (Table 1). Clinical presentations were
nonspecific, and the most common symptoms included
lethargy and dysarthria, which were present in 83% and
67% of patients, respectively (Table 2). Five of the 6 pa-
tients had chronic alcoholism, 1 had hyponatremia, and
1 had undergone a liver transplantation (Table 3). All
patients had improvement in their clinical conditions at
the time of hospital discharge (Table 4).

CASE PRESENTATION

BW is a 32-year-old American Indian female with a past
medical history of heavy alcohol use who reported rectal
bleeding of approximately 5 months duration, dizziness,
and palpitations. On admission, she complained of leth-
argy and was found to be pale with a hemoglobin level of
2.6 g/dL and normal serum electrolytes. She underwent
2 esophagogastroduodenoscopies and a colonoscopy and
was found to have hemorrhoids and small esophageal
varices with no evidence of past or current bleeding. She
was readmitted 5 days post-discharge with worsening leg
edema and general malaise. Despite adequate blood trans-
fusion, she continued to be lethargic and ataxic and had
significant psychomotor slowing without focal neurologi-
ical findings. A magnetic resonance imaging (MRI) scan of
the brain showed central and extrapontine myelinolysis
(Figure 1). The patient was managed conservatively, and
after 10 days of inpatient care she was transferred to a drug
and alcohol treatment center for 3 months. Subsequent
follow-up showed complete clinical recovery.

DISCUSSION

Epidemiology

CPM and ODS are rare medical conditions. The exact
incidence of these conditions is unknown and has
been derived primarily from autopsy series. In a series
of 3548 consecutive autopsies in adults with CPM or
ODS, the typical lesions were found in 9 (0.25%) of the
cases.3 The incidence rates are highest in alcoholics and
liver transplant recipients, in whom a 30% postmortem
incidence rate has been reported.4 CPM and ODS have
their peak incidence in individuals between the ages of
30 and 50. However, children can also be affected.5 The
findings of this series are in agreement with the above-
mentioned epidemiological data.

Subtypes

There are 3 subtypes of brain demyelinating disease: (1)
CPM, in which the lesion is confined to the pons; (2)
extrapontine myelinolysis (EPM), in which the lesions
are confined to the basal ganglia, cerebrum, and cerebel-
hum; and (3) ODS, in which CPM and EPM lesion sites
are both present.
Etiology
CPM has traditionally been associated with rapid correction of hyponatremia, but the etiology has not been clearly established. In a case series of 442 patients, Lampl and Yazdi found that 39.4% were alcoholics, 21.5% had been treated for hyponatremia, and 17.4% were liver transplant recipients. Alcoholism, chronic malnutrition, and sodium imbalances are the primary conditions reported with CPM. Alcoholism has been reported in as many as 78% of the cases. More recent studies have implicated rapid correction of hyponatremia and hypernatremia as the cause of CPM or ODS. Kleinschmidt-DeMasters and Norenberg were the first to describe the increased risk of CPM with rapid correction of hypernatremia. However, alcoholism alone can cause CPM, since this condition has been described in alcoholic patients who were normotremic, as was the case in 5 of 6 of the patients in this series. Hypokalemia in association with hyponatremia has also been implicated. These findings have led to the recommendation of correcting hypokalemia in patients prior to correcting hyponatremia.

The patients described in our series were predominantly chronic alcoholics (5 out of 6 patients) (Table 3). The importance of liver transplantation in the pathogenesis of CPM can be further supported by the presence of a liver transplant patient in our 6-patient series.

Table 3. Underlying and Concomitant Diseases of 6 Patients with CPM or ODS

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Cases/Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic alcoholism</td>
<td>5/6</td>
<td>83</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2/6</td>
<td>33</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2/6</td>
<td>33</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2/6</td>
<td>33</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>1/6</td>
<td>17</td>
</tr>
<tr>
<td>Pulmonary infections</td>
<td>1/6</td>
<td>17</td>
</tr>
<tr>
<td>Had a liver transplant</td>
<td>1/6</td>
<td>17</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>1/6</td>
<td>17</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1/6</td>
<td>17</td>
</tr>
</tbody>
</table>

CPM=central pontine myelinolysis; ODS=osmotic demyelination syndrome

Table 4. Clinical Outcomes of 6 Patients with CPM or ODS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Cases/Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>6/6</td>
<td>100</td>
</tr>
<tr>
<td>Had clinical follow-up</td>
<td>4/6</td>
<td>67</td>
</tr>
<tr>
<td>Follow-up MRI</td>
<td>1/6</td>
<td>17</td>
</tr>
<tr>
<td>Discharged to detoxification facility</td>
<td>3/4</td>
<td>75</td>
</tr>
<tr>
<td>Discharged to home</td>
<td>1/4</td>
<td>25</td>
</tr>
</tbody>
</table>

CPM=central pontine myelinolysis; MRI=magnetic resonance imaging; ODS=osmotic demyelination syndrome

This is in agreement with prior case series. However, the limited series may not be truly representative.

Pathogenesis
The pathogenesis of CPM is unknown, but theories such as the osmotic hypothesis of CPM have implicated hyponatremia and its rapid correction in some cases. It is postulated that cells conditioned to a hypoosmotic hyponatremia environment may have a decreased adaptive capacity to osmotic stress. Ashrafian and Davey proposed that individuals susceptible to CPM, such as those with chronic alcoholism, have inadequate energy provisions, as well as other factors that result in a pro-apoptotic drive. The predilection of the myelinolysis to the pons is thought to be a result of the grid arrangement of the oligodendrocytes in the base of the pons, which limits their mechanical flexibility and, therefore, their capacity to swell. During hyponatremia these cells can only adapt by losing more ions instead of swelling, making them prone to damage when sodium is replaced. Proximity to the extensively vascularized gray matter makes the pons particularly susceptible to damage caused by vasogenic edema and myelinotoxic substances from the vessels.

Clinical Presentation
The clinical presentation of CPM is highly variable, as evidenced by the presenting signs and symptoms of our patients (Table 2). Patients typically experience a rapidly evolving paraparesis or quadriplegia and pseudobulbar symptoms such as dysarthria and dysphagia. They may present with “locked-in syndrome,” in which intellectual activity is preserved but cannot be expressed because of a total incapacity to produce voluntary responses. Less often, CPM manifests with ataxia, other movement disorders, or behavioral symptoms. Clinical manifestations range from asymptomatic to coma depending on the location of the lesions. The severity of the clinical presentation does not correlate with the size of the lesions. The broad range of clinical manifestations, some of which are very protean, can make the diagnosis difficult. A high index of suspicion should be maintained in the appropriate clinical setting.

Diagnosis
Diagnosis of CPM is based on clinical suspicion and is confirmed by imaging studies. MRI is the primary method for diagnosis and is superior to computerized tomography (CT). During the acute phase, symmetrical and hypointense lesions on a T1-weighted MRI can be identified. In comparison, during the subacute phase there are symmetrical and hypointense lesions on T2-weighted images. Lesions on MRI may appear days to
weeks after the onset of symptoms and may resolve, in some cases, over a period of months.

Management
The most important step in the management of CPM is recognizing the patient at risk and preventing rapid correction of hyponatremia—especially chronic, severe hyponatremia. Once a diagnosis is made, the management of CPM is mainly supportive while preventing secondary complications that could lead to severe morbidity and mortality.

Four treatment modalities have been reported, including (1) thyrotropin-releasing hormone (TRH),21 (2) methylprednisolone,22 (3) plasmapheresis,23 and (4) immunoglobulins.24 Chemaly and colleagues administered TRH in a daily dose of 0.6 mg intravenously for 6 weeks to a 13-year-old girl who had been diagnosed with EPM after surgery for extradural hematoma that had been followed by hyponatremia.21 They reported clinical improvement a few days after administration of the hormone that continued until complete recovery. In 1993, Konno and colleagues reported the use of TRH in a 65-year-old man who had undergone mitral valve replacement after rupture of a chorda tendinae whose postoperative course was complicated by hypernatremia, tetraplegia, and coma.23 He was found to have a low-density area in the central pons on CT imaging that was suggestive of CPM (later confirmed by MRI). His central nervous system symptoms dramatically improved after administration of TRH tartrate, and he recovered without neurological deficit.

Methylprednisolone, with or without plasmapheresis, used in a daily dose of 375 mg intravenously has been found to be effective for the treatment of CPM.22 Nishino and colleagues reported a case of CPM associated with hyponatremia that improved with administration of methylprednisolone and correction of hyponatremia.24 Finsterer and colleagues assert that intravenous immunoglobulins are effective due to the reduction in myelinotoxic substances, the formation of antimyelin antibodies and support of remyelination.25 They reported a case of a 48-year-old patient who developed CPM after spontaneous normalization of hyponatremia. He received intravenous immunoglobulin, and after 2 days he noted improvement in his symptoms.

Plasmapheresis has also been applied to the treatment of CPM. Bibl and colleagues reported 3 cases of CPM treated with plasmapheresis.22 The first case was a 29-year-old female with chronic alcohol abuse and hyponatremia. She developed tetraparesis and abnormal bulbar movements after correction of her hyponatremia. Plasmapheresis was performed daily for 4 days followed by twice weekly treatments for 3 weeks, resulting in a total of 24,700 mL of plasma exchanged. Tetraplegia resolved within 2 months. However, she had salient signs of ataxia at 1 year. The second case reported by Bibl and colleagues was of a 20-year-old female with anorexia nervosa and hyponatremia. She became somnolent with spastic tetraparesis after the correction of her hyponatremia over 5 days. She underwent 3 sessions of plasmapheresis for a total of 5234 mL of plasma exchange. She was able to walk 1 month later. The third patient was a 30-year-old female with chronic alcoholism and mild hyponatremia who developed CPM and was subsequently treated with 7 weeks of plasmapheresis for a total of 18,270 mL of plasma exchange. Her mild ataxia improved to remission after 12 months.

The exact mechanism of action of TRH, corticosteroids, and plasmapheresis is unknown, and no randomized studies have been conducted to confirm the efficacy of any of these treatment modalities. In the absence of randomized trials, we cannot recommend any of these treatments. A conservative approach, with treatment of the precipitating or underlying conditions and appropriate supportive care in severe cases, may be justified in the absence of studies confirming the efficacy of the above-mentioned treatments. The patient described in our case presentation had a remarkable turnaround during inpatient alcohol detoxification. She continues to do well 2 years after the initial diagnosis of CPM was made.

Clinical Course/Prognosis
Early reports of CPM indicated almost a 100% mortality rate within 3 months following hospital admission.26 Lohr reviewed 74 patients with CPM after treatment for hyponatremia between 1962 and 1994 and found 34 deaths and a “significant neurological deficit” in most of the remaining patients.13 Recent studies of CPM and EPM report a milder clinical course without substantial neurological deficits in survivors. All of our patients improved (Table 4), which is in agreement with more recent case series.19

Meng and Jorg retrospectively evaluated the data of 44 patients with CPM and EPM treated between 1990 and 1996.10 Of this cohort, 42 were chronic alcoholics. Follow-up data were available on 34 of the patients for a period ranging between 3 weeks and 44 months. Of the 34 patients, 32 survived the acute episode. Eleven of the 32 patients had no functional deficits, 11 had minor neurological deficits, and 10 had severe neurologic deficits. Prognosis was not worse in patients with both CPM and EPM as compared to those with CPM alone. Clinically,
there was no statistically significant relationship between the most severe neurological symptoms and the course of the disease, nor between concomitant diseases and the course of the disease. Neuroradiologically, there was a slight regression of MRI findings over the course of the disease. However, there was no correlation between the size of the pontine lesion on MRI and the clinical course.

**CONCLUSION**

CPM and EPM are rare demyelinating diseases of the pons and extrapontine sites. Management of these conditions involves recognizing the patient at risk, preventing rapid correction of hyponatremia, making a prompt diagnosis, and managing the associated complications. Decreasing mortality rates reflect earlier recognition, prevention, and treatment of associated complications.

**ACKNOWLEDGMENTS**

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**REFERENCES**