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# Pontine and Extrapontine Myelinolysis: Risk Factors and Characterization of Patients Diagnosed in Three Decades in a Tertiary Center

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## ABSTRACT

**Background:** Osmotic demyelination syndrome is a rare neurological disorder caused by damage to the myelin sheath of oligodendrocytes, typically due to a rapid increase in serum osmolarity. **Objective:** The objective of the study was to investigate the factors associated with the development of pontine or extrapontine myelinolysis. **Methods:** A retrospective, observational study which included patients with magnetic resonance imaging-confirmed diagnosis of pontine and extrapontine myelinolysis from 1990 to 2024 at a referral hospital in Mexico City. **Results:** Fourteen patients were included; the median age was 49 years, and 35.7% were men. Regarding comorbidities, diabetes was the most frequent (35.7%), followed by liver cirrhosis, malnutrition, and chronic alcoholism. Significantly, hyponatremia was found in 11 patients (78.5%), being severe in 42.8% of the patients. Other frequent biochemical abnormalities were hypokalemia (42.8%) and hypomagnesemia in 5 (35.7%). Sodium overcorrection occurred in 50% of patients, and the 90-day mortality rate was 28.5%. **Conclusions:** Electrolyte disturbances, particularly hyponatremia, were common in this population, along with the comorbidities traditionally associated with this condition. Although neurological sequelae and mortality have decreased over time, they remain present in 64% and 28.5% of patients, respectively. (REV INVEST CLIN. 2025;77(1):1-5)

**Keywords:** Pontine myelinolysis. Extrapontine myelinolysis. Hyponatremia. Epidemiology. Mexico.

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## INTRODUCTION

Osmotic demyelination syndrome is a rare neurological disorder caused by damage to the myelin sheath of oligodendrocytes in the brain commonly due to a rapid increase in serum osmolarity[1], with central pontine myelinolysis being the classic presentation[2], while the extrapontine form occurs in the white matter of the cerebral hemispheres[3].

While most of the earliest publications (up to the mid-1980s) described chronic alcohol consumption and alcohol withdrawal as the most common risk factors (> 40%), subsequently, hyponatremia (low sodium) has been listed as the most common cause of this entity with prevalences ranging from 30% to 78% of cases. Severe hyponatremia (serum sodium levels < 120 mmoL/L) is usually present in about 47% of cases; however, most patients have additional risk factors, each of which alone can trigger osmotic demyelination syndrome. Severe hypokalemia (low potassium) is especially important, mainly in patients admitted to intensive care units[4,5].

On the other hand, the prevalence of this complication has been estimated in 0.25 to 0.5% in the general population, and up to 10% in patients undergoing liver transplantation[1,6]. The prognosis for osmotic demyelination syndrome is typically severe. Since there is no specific treatment, it is focused on relieving symptoms. Patients usually require prolonged neurorehabilitation, and symptoms have been described as irreversible or partially reversible, with mortality rates between 12% and 30%, with a significant decrease in recent years[1,3].

We evaluated the risk factors, as well as clinical and epidemiological characteristics of Mexican patients diagnosed with pontine and extrapontine myelinolysis in a tertiary center over three decades.

## METHODS

This is a retrospective, observational study, which included patients with magnetic resonance imaging (MRI) confirmed diagnoses of pontine and/or extrapontine myelinolysis in a tertiary care hospital in Mexico City over a period of three decades. We searched the physical and electronic clinical records of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán for single cases diagnosed in the period from 1990 to 2024. First, we searched for the International Classification of Diseases-10$^{th}$ edition codes for central nervous system (CNS) demyelinating disorders, followed by a search limited to the terms central pontine myelinolysis, extrapontine myelinolysis, and osmotic demyelination. Regarding demographic variables, age, sex, comorbidities (alcoholism, malnutrition, history of liver transplantation, and diabetes), and medications before admission were collected. Laboratory data included were the presence of hyponatremia, lower sodium, higher sodium, presence of hypokalemia, hyperglycemia, and imaging findings in brain MRI. Clinical variables included clinical presentation, clinical outcome, and mortality. Inclusion criteria were patients ≥ 18 years with osmotic demyelination syndrome according to clinical manifestations and diagnosis of pontine/extrapontine myelinolysis, confirmed by typical features in neuroimaging or histopathological studies. Exclusion criteria were patients diagnosed with other demyelinating diseases of the CNS, patients with suspected diagnosis in whom an MRI study ruled out pontine or extrapontine myelinolysis or patients with other differential diagnosis that would explain the clinical picture referred in the file by the treating physician.

### Statistical analysis

For continuous variables, their distribution was evaluated using the Kolmogorov–Smirnov test. Descriptive statistics are expressed as number (percentage), mean (standard deviation) and median (interquartile range), as appropriate. In addition, we compared the characteristics of our series with an Australian report, for which the $X^2$ or Fisher's exact test were used as appropriate. All statistical tests were bilateral and a p = 0.05 was considered statistically significant. All analyses were performed with Statistical Packages for the Social Sciences 26.0 (IBM, Armonk, NY, USA).

## RESULTS

The present study included 14 patients with the diagnosis; demographic data of the patients are shown in Table 1. The median age was 49 years, and 35.7% were men. Regarding comorbidities, diabetes was a frequent finding (5; 35.7%), liver cirrhosis and

Table 1. Demographic characteristics and laboratory and imaging findings in patients diagnosed with pontine and extrapontine myelinolysis

| Characteristic | n = 14 (%) |
|---|---|
| Demographics | |
| Male | 5 (35.7) |
| Age at diagnosis (years) | 49 (22-65) |
| Comorbidities | |
| Malnutrition | 4 (28.5) |
| Alcoholism | 3 (21.4) |
| Diabetes | 5 (35.7) |
| Liver cirrhosis | 4 (28.5) |
| Chronic kidney disease | 3 (21.4) |
| Liver transplantation | 1 (7.1) |
| Laboratory findings | |
| Hyponatremia | 11 (78.5) |
| – Mild (130-134 mmoL/L) | 4 (28.5) |
| – Moderate (125-129 mmoL/L) | 1 (7.1) |
| – Severe (< 125 mmoL/L) | 6 (42.8) |
| – Overcorrection (> 8 mmoL/24 h) | 7 (50) |
| Sodium correction rate (mmoL/24 h) | 7.5 (3-17) |
| Hypokalemia | 6 (42.8) |
| Hypophosphatemia | 1 (7.1) |
| Hypocalcemia | 2 (14.2) |
| Hypomagnesemia | 5 (35.7) |
| Hyperglycemia | 1 (7.1) |
| Use of diuretics | 5 (35.7) |
| MRI findings | |
| Pontine myelinolysis | 14 (100) |
| Extrapontine and pontine myelinolysis | 9 (64.2) |

Data are reported in n (%) or median and interquartile range.

malnutrition were found in 4 patients (28.5%), and chronic alcoholism was found in 3 patients (21.4%). Of relevance, hyponatremia was found in 11 patients (78.5%), being severe in 42.8% of patients, and overcorrection of sodium levels (> 8 mmoL/24 h) occurred in 50% of the included patients. Other frequent biochemical abnormalities were hypokalemia in 6 (42.8%) and hypomagnesemia in 5 (35.7%).

Table 2. Clinical manifestations and outcomes in patients diagnosed with pontine and extrapontine myelinolysis

| Characteristic | n = 14 (%) |
|---|---|
| Alteration of alertness/ encephalopathy | 12 (85.7) |
| Seizures | 3 (21.4) |
| Locked-in syndrome | 1 (7.1) |
| Extrapyramidal syndrome | 1 (7.1) |
| Language impairment | 3 (21.4) |
| Weakness | 4 (28.5) |
| Swallowing disorders | 2 (14.2) |
| Neurological sequelae | 9 (64.2) |
| Death within 90 days | 4 (28.5) |

Data are reported in n (%).

In the MRI study, all patients presented pontine involvement and 9 (64.2%), concomitant extrapontine alterations.

Regarding the clinical presentation, the manifestations were varied and are summarized in table 2. Of the 14 patients, the most common presentation was altered consciousness/encephalopathy (12; 85.7%), followed by weakness (4; 28.5%), seizures, and language impairment (3; 21.4%). Other manifestations included locked-in syndrome, hyporeflexia, facial paralysis, extrapyramidal syndrome, and aphasia. At follow-up, neurological sequelae were documented in 9 patients (64.2%) and there were 4 deaths at 90 days (28.5%).

## Comparison with other populations

Regarding the comparison of our series with other internationally documented data, in the Ambati et al.[5] series, with criteria similar to those presented in this review, we found a lower incidence of alcoholism, without differences in other factors associated with the development of myelinolysis (Table 3). With respect to biochemical findings, the most frequent disorder was hyponatremia; however, in the Australian series other electrolyte disturbances were documented more frequently such as hypokalemia and hypophosphatemia. We did not find significant differences in clinical outcomes and mortality.

Table 3. Demographic characteristics in a Mexican population compared with those reported in the international literature (case series reported in Australia)

| Characteristic | Our series n = 14 (%) | Ambati et al.[5] n = 15 (%) | p |
|---|---|---|---|
| Male | 5 (35.7) | 10 (66.6) | 0.096 |
| Comorbidities | | | |
| Malnutrition | 4 (28.5) | 9 (60) | 0.089 |
| Alcoholism | 3 (21.4) | 10 (66.7) | 0.014 |
| Diabetes | 5 (35.7) | 4 (26.7) | 0.700 |
| Liver cirrhosis/liver transplantation | 4 (28.5) | 3 (20) | 0.682 |
| Laboratory findings | | | |
| Hyponatremia | 11 (78.5) | 14 (93.3) | 0.330 |
| – Mild (130-134 mmoL/L) | 4 (28.5) | 4 (26.7) | 1.000 |
| – Moderate (125-129 mmoL/L) | 1 (7.1) | 8 (53.3) | 0.014 |
| – Severe (< 125 mmoL/L) | 6 (42.8) | 2 (13.3) | 0.109 |
| – Overcorrection (> 8 mmoL/24 h) | 7 (50) | 2 (13.3) | 0.050 |
| Hypokalemia | 6 (42.8) | 14 (93.3) | 0.005 |
| Hypophosphatemia | 1 (7.1) | 9 (60) | 0.005 |
| MRI findings | | | |
| Pontine myelinolysis only | 5 (35.7) | 9 (60) | 0.096 |
| Pontine and extrapontine myelinolysis | 9 (64.2) | 5 (33.3) | 0.096 |
| Clinical outcomes | | | |
| Neurological sequelae | 9 (64.2) | 12 (80) | 0.427 |
| Death within 90 days | 4 (28.5) | 2 (14.3) | 0.390 |

## DISCUSSION

In the present study, we documented that electrolyte disturbances, especially hyponatremia, are frequently found in this population; overcorrection of hyponatremia (> 8 mEq/L in 24 h) was only present in 50% of the patients. We know that pontine and extrapontine myelinolysis is a rare but serious neurological condition, frequently associated with rapid hyponatremia corrections. Historically, current guidelines recommend a sodium increase of no more than 8-10 mmoL/L in the first 24 h and no more than 18 mmoL/L in the first 48 h to minimize the risk of demyelination. However, several studies have identified other risk factors that predispose patients to this condition, emphasizing some such as renal failure, liver disease, underlying organ transplants, as well as the use of certain medications and malnutrition[2,7]. In this study, such comorbidities were documented in this population which could have contributed to a greater susceptibility to this complication. The clinical characterization of patients with osmotic demyelination syndrome can be varied and depends largely on the extent and location of demyelination[8,9]. Symptoms may include altered consciousness, dysarthria, dysphagia, paraparesis or tetraparesis, and in severe cases, coma. We document altered consciousness as the main clinical feature at diagnosis. The diagnosis of pontine and extrapontine myelinolysis is based on a combination of clinical evaluation and imaging techniques, especially MRI.

In conclusion, and accurate identification is crucial to improve clinical outcomes and avoid serious complications[10]. We found that all of our patients presented pontine myelinolysis by MRI study; however, 64% of patients also presented data of extrapontine

involvement. Thiscould be associated with other uncontrolled electrolytes, as previously mentioned, and even with other non measured metabolites associated with a rapid increase in serum osmolarity. The literature suggests that early identification through advanced imaging techniques can significantly reduce the morbidity and mortality associated with these conditions, since a rapid intervention based on early MRI diagnosis improves the clinical outcome in patients with osmotic demyelination[10]. In our study, the estimated mortality was close to 30%, with sequelae in more than 60% of the population studied.

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