Current Concepts in Pontine Myelinolysis: Review of Literature

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Abstract
Pontine myelinolysis (PM) is a neurological disorder represented by demyelination of the pons. It can be classified into central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM). Onset of PM is controversial, however etiology is believed to occur by rapid correction of hyponatremia. Epidemiology, clinical diagnosis, and neurological complications of PM is a rare disorder. Onset of hyponatremia due to irrigation fluid is emphasized. Differential diagnosis, histopathology, connection with autonomic neuropathy, and magnetic resonance image findings of PM is reviewed. Prevention and treatment of hyponatremia to avoid side effects and pharmacological treatments for PM is discussed. This review is to expand on the information already provided in literature and update on current literature.

Keywords: Pontine Myelinolysis; Osmotic demyelination syndrome; Central pontine myelinolysis; Extrapontine myelinolysis; Hyponatremia; Demyelination; Prostate

Abbreviations: PM: Pontine Myelinolysis; ODS: Osmotic Demyelination Syndrome; CPM: Central Pontine Myelinolysis; EPM: Extrapontine Myelinolysis; BBB: Blood Brain Barrier; MRI: Magnetic resonance imaging; GABA: Gamma-aminobutyric acid

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Introduction
Pontine myelinolysis (PM) was first described in 1959 by Adams et al. in alcoholic patients [1]. Also known as osmotic demyelination syndrome (ODS), PM is subdivided into central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) [2]. Each is identified at the level of demyelination either centered within the pons [1] or outside the pons [3], respectively. While the etiology of ODS is poorly understood, it is believed that rapid correction of sodium in chronic hyponatremia is implicated as primary factor [1].

Epidemiology of pontine myelinolysis
ODS, though uncommon, has been reported at a rate of 0.4-0.56% for patients admitted to neurology services and 0.05% of all admitted in a general hospital [4-6]. Underdiagnosis of ODS has been reported in recent literature; Newell et al. identified 0.3-1.1% of patients with unsuspected CPM during autopsies, with an even greater percentage of CPM in patients with liver transplant and chronic liver disease [7].

Clinical diagnosis of pontine myelinolysis
When trying to diagnosis a patient with PM, examining physical symptoms and neurological complications may often be the simplest route. The most common symptoms seen in PM patients are tremor and quadriplegia [8-12] as well as depressed level of consciousness [13]; additional clinical diagnosis and neurological complications are outlined in Tables 1 and 2, respectively. In patients suspected of early PM, the new concept of fundoscopy may reveal optic disc changes suggestive of raised intracranial hypertension.

Pathogenesis of pontine myelinolysis
Despite PM’s relatively ambiguous pathogenesis, it is believed that rapid correction of hyponatremia plays a pivotal role [28]. Hyponatremia causes glial cells to swell via selective aquaporin channels [29]. Treatment of chronic hyponatremia, using a hypertonic saline solution, causes brain cell dehydration and the loss of vital electrolytes in addition to organic osmolytes such as myo-inositol, taurine, glutamine, glutamate, creatine, phosphocreatine, and glycerophosphorylcholine [30]. Failure to
compensate for increasing plasma tonicity within cells results
in osmotic stress [31], all the while preventing the reabsorption
of organic osmolytes into the cell [30]. According to studies by
Rojiani et al., [32,33], the opening of the blood brain barrier
(BBB) and the generation of edema may play a role in the early
stages of the disease. Stress on the BBB as a result of osmotic
shrinkage results in the opening of tight junctions [34]. This is of
particular concern in oligodendrocytes, which appear to be the
most susceptible cells to this form of damage [11]. Todd et al.,
suggested that plasminogen activator, complement proteinase,
cytokines, immunoglobulins, and neural proteases released from
endothelial cells may lead to oligodendrocyte degeneration [35],
ultimately causing the destruction of myelin [11] (Figure 1).

Onset of Hyponatremia

Hyponatremia is defined by the excess of water in relation to
the serum sodium concentration; Table 3 depicts its severity
levels [36]. Absorption of irrigation fluid, a surgical necessity for
improving operating field vision, is known to induce iatrogenic
hyponatremia [37]. The irrigation fluid must be generally
electrolyte free to allow cutting with a resectoscope, despite a
danger of absorption [37]. Glycine 1.5%, mannitol, or sorbitol are
common solutes added to decrease hypo-osmolality and prevent
hemolysis in the event of reabsorption [37]. For absorption to
occur, the driving force of fluid must exceed the venous pressure
of approximately 1.5 kPa [38]. Fluid absorption can occur in all
operations utilizing irrigation fluid. Irrigation fluid is used most
commonly in transurethral resection of the prostate (TURP)
and transcervical resection of the endometrium (TCRE) [37]. Absorption can range between 300-1000 mL in 8% of TURP operations [39] and approximately 450 mL in TCRE procedures [40]. Moreover, photoselective vaporization of the prostate via green light laser surgery is a minimally invasive technique [41] that delivers more advantages than TURP [42]. However, absorption of irrigation fluid is still possible in patients who undergo high power 532 nm laser vaporization of the prostate [43]. Fluid absorption can elicit cardiopulmonary and neurological symptoms, while ethanol breath tests yield early detection [43].

Etiology of pontine myelinolysis

Rapid correction of hyponatremia is one of the many potential causes of PM. Uchida et al., explains where a patient develops CPM secondary to liver transplant [44]. Wadhwa et al., identified a case where an alcoholic patient showed signs of EPM [45]. CPM can also be a rare manifestation of Wilson’s disease [46] and celiac disease [8]. According to Wu et al., EPM can arise from primary adrenal insufficiency. This author described a 49 year old female who presented with primary adrenal insufficiency. The patient was given an isotonic saline solution to treat for adrenal insufficiency and hyponatremia. Rapid correction showed demyelination of the bilateral basal ganglia and the thalamus, using MRI [47]; additional causes are outlined in Table 4.

Differential diagnosis of pontine myelinolysis

According to Falini et al., acute multiple sclerosis lesions can be seen as hyperintense lesions on T2-weighted sequences and accompanied by BBB breakdown showing contrast on T1-weighted images. This is sometimes perceived as PM, as demyelination is implicated at the pons, basal ganglia, midbrain, thalamus, and subcortical white matter [58]. Using magnetic resonance imaging (MRI), PM is marked by prolongation of T1 and T2 relaxation times in myelinolytic regions [58].

Histopathology of pontine myelinolysis

Intramyelinitic splitting, vacuolization, and rupture of myelin sheaths are key in identifying histopathological finding of an individual with CPM [59]. Progression of CPM results in macrophages findings at the site myelin debris [59]. Pietrini et al., identified an acute stage of demyelination and large macrophagic infiltration, but no significant inflammatory reaction [60].

Autonomic neuropathy and pontine myelinolysis

Autonomic neuropathy and PM can be found occurring simultaneously in patients. A 2008 case study by Tilikete et al., identified a 51 year old patient with primary position upbeat nystagmus and internuclear opthalmoplegia. The diagnosis, using MRI, showed a demyelination of the pons may have resulted in this action [61]. A 1999 article by Susa et al., discussed a 29 year old woman with acute intermittent porphyria-an autosomal dominant disease caused by a deficiency of porphobilinogen deaminase-suffered severe hyponatremia and was treated with heme arginate. MRI showed CPM and EPM, and cortical laminar necrosis, all of which are not common in acute intermittent porphyria [62].

Magnetic resonance imaging of pontine myelinolysis

MRI has streamlined the diagnosis of PM by tracing the evolution of the lesion and pairing its progression or regression with clinical features [63]. Prominent signal characteristics include T1-hypotensive, T2-hypertensive, and FLAIR-hypertensive [5]. Table 5 highlights several brain regions affected by PM.

Prevention and treatment of pontine myelinolysis

Several options surround the prevention and treatment of PM. A hallmark of prevention is proper management of hyponatremia post-absorption of irrigation fluid. Hyponatremia can be treated using hypertonic saline solution [30]. Treatment can, however, pose a challenge as rapid correction can lead to PM [3]. Gradually increasing the sodium concentration, from 4-6 mmol.L$^{-1}$ in any 24 hour period, is the most favorable therapy to treat a patient with severe hyponatremia while preventing any unwanted side effects [65].

A unique situation in which rapid correction of hyponatremia without consequence of PM may be embraced by azotemic, patients with large amounts of nitrogenous waste products in blood, patients [66]. Dhrolia et al., conducted a study on 52 azotemic patients, who had undergone hemodialysis to rapidly treat hyponatremia [66]. Despite the known assumption that rapid correction will elicit PM, MRI verified that none of the

<table>
<thead>
<tr>
<th>Levels</th>
<th>Serum concentration: mmol•L$^{-1}$</th>
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<tbody>
<tr>
<td>Severe</td>
<td>&lt; 120</td>
</tr>
<tr>
<td>Moderate</td>
<td>120-124</td>
</tr>
<tr>
<td>Mild</td>
<td>125-134</td>
</tr>
<tr>
<td>Normal</td>
<td>135-144</td>
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</table>

Table 3 Severity of hyponatremia.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver transplant</td>
<td>[44,48-50]</td>
</tr>
<tr>
<td>Alcohol</td>
<td>[45,51]</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>[52]</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>[53]</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>[54]</td>
</tr>
<tr>
<td>Hypermartenia</td>
<td>[55,56]</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>[46]</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>[55,57]</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>[8]</td>
</tr>
<tr>
<td>Primary Adrenal Insufficiency</td>
<td>[47]</td>
</tr>
</tbody>
</table>

Table 4 Etiology of pontine myelinolysis.

| Magnetic Resonance Imaging of Brain Regions for Pontine Myelinolysis Diagnosis |
|-------------------------------|------------------|
| Brain Region                  | Reference        |
| Pons                          | [23,49,51,56,64]|
| Basal ganglia                 | [13,22,26]       |
| Thalamus                      | [26]             |
| Cerebellum                    | [26]             |
| Middle cerebellar peduncle    | [44]             |
| Corpus callosum               | [57]             |
52 patients with azotemia developed neurological conditions. Azotemia may protect the brain from osmotic demyelination by rapidly changing urea concentration. Urea can act as an effective osmole in dialysis disequilibrium syndrome [66].

A separate method for treating PM involves the administration of intravenous immunoglobin (IVIg). Murthy et al., highlighted three PM cases in which the patient received IVIg over the course of a few days and began to recover [67]. Despite the unclear mechanism, a possible explanation involves the reduction of myelinotoxic substances and promotion of remyelination [68]. Plasmaphersis (PS) is another option in treating PM. Saner et al., identifies a patient, who underwent liver transplant and developed CPM. The patient was immediately placed PS and IVIg for six days. The patient showed signs of recovery after the treatment [69]. It is believed that PS may also reduce myelinotoxic substances, thereby leading to clinical improvement [69]. Table 6 provides additional pharmacological treatment options.

**Conclusion**

Pontine myelinolysis (PM) develops primarily from rapid treatment of hyponatremia, but also occasionally from liver transplantation and alcohol abuse. The effect of PM can be seen through histological examination and MRI-deduced regional brain effects. Upon treating chronic hyponatremia with hypertonic saline, the disequilibrium of organic osmolytes may play a key role in the pathogenesis of PM. Hyponatremia is caused from absorption of irrigation fluid during operations such as transurethral resection of the prostate (TURP). Prevention of PM must be conducted by gradually increasing sodium concentration 4-6 mmol.L⁻¹ in any 24-hour period. Additional PM treatment mandates the use of immunoglobulin, plasmaphersis, or select neurological drugs.

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**Compliance with Ethical Standards**

The authors declare they have no conflict of interest.

<table>
<thead>
<tr>
<th>Drug Name or Class</th>
<th>Identity/Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>Dopamine precursor that can cross the BBB to increase the concentration of dopamine.</td>
<td>[6,70-72]</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Weak antagonist of N-methyl-D-aspartate-type glutamate receptor that blocks reuptake of dopamine.</td>
<td>[72]</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Blocks acetylcholine from binding to its receptor in the central and peripheral nervous system.</td>
<td>[6,73,74]</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Dopamine agonist that activates dopamine D₂, D₃, and D₄ receptors.</td>
<td>[75]</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Benzodiazepine drug mainly prescribed for epilepsy and panic disorder.</td>
<td>[6,76]</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Derivative of gamma-aminobutyric acid (GABA). It is an agonist of GABA₄ receptors used for treating spastic movement and addiction.</td>
<td>[6,11,77]</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>Neurotoxin produced from bacterium Clostridium botulinum that prevents the release of acetylcholine.</td>
<td>[6]</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Dopamine agonist. Potent agonist at dopamine D₂ receptors and various serotonin receptors.</td>
<td>[78]</td>
</tr>
<tr>
<td>Tiapride</td>
<td>Selectively blocks dopamine D₂ and D₃ receptors. Treats various neurological and psychiatric disorders.</td>
<td>[79]</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Antipsychotic drug and dopamine antagonist.</td>
<td>[79]</td>
</tr>
<tr>
<td>Pergolide</td>
<td>Dopamine receptor agonist that binds to dopamine D₂ and D₃ receptors and various serotonin receptors.</td>
<td>[72]</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Antipsychotic drug.</td>
<td>[76]</td>
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</tbody>
</table>
References


