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Topical Review

Osmotic Demyelination Syndrome in Children

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ABSTRACT

Osmotic demyelination syndrome is an acute demyelination process that usually occurs several days following an osmotic stress. This syndrome is rare in adults (0.4% to 0.56%) and even more uncommon in children. We performed a review of all reported pediatric osmotic demyelination syndrome patients from 1960 to 2018. Among all 106 cases, 49 presented with isolated central pontine myelinolysis, 30 with isolated extrapontine myelinolysis, and 27 with combined central pontine myelinolysis and extrapontine myelinolysis. There was no gender preponderance, and the highest prevalence was noted between the ages one and five years. Magnetic resonance imaging remains the diagnostic modality of choice, and diffusion tensor imaging is now increasingly used for prognostication in osmotic demyelination syndrome. Sixty percent of the children had a complete neurological recovery. Current management of osmotic demyelination syndrome in children consists of supportive medical care, steroids, and intravenous immunoglobulin. Our review of the literature supports the hypothesis that steroids and immunoglobulins are potentially helpful, although additional controlled studies are needed.

Introduction

Osmotic demyelination syndrome (ODS) is an acute demyelination process that usually occurs several days following a rapid rise in serum osmolality. ODS was originally described in 1959 by Adams et al.,[1] who recognized a peculiar and unique demyelination occurring in the central pons in individuals with alcoholism and malnutrition and labeled it *central pontine myelinolysis* (CPM). Since this original description, the demyelination process following osmotic stress involving locations outside the pons has been termed *extrapontine myelinolysis* (EPM).[2] As both CPM and EPM share a common histology, they are known as ODS.

Prevalence

ODS is rare, reported in 0.4% to 0.56% of patients admitted to a neurology service and 0.06% of all admissions to general medical and neurology services.[3-5] The true incidence of ODS is actually higher (0.3% to 1.1%) owing to the presence of asymptomatic CPM as identified by autopsy.[6]

ODS in children is even more uncommon than it is in adults. We performed a review of all reported pediatric ODS cases from 1960 to 2018 based upon a search of English language literature using Pubmed and Google Scholar databases and the following search terms: *osmotic demyelination syndrome and child, central pontine myelinolysis, and extrapontine myelinolysis*. A total of 106 pediatric cases with ODS were noted. It is probable that this number is an underestimate owing to the presence of asymptomatic and unreported cases. Among all 106 cases reported, 46% (49) children presented with isolated CPM, 28% (30) with isolated EPM, and the rest, 25% (27), with combined CPM and EPM. The highest prevalence of ODS is between the ages one and five years (35%), and a decline in its occurrence is noted with increasing age (Fig 1). The lowest prevalence of ODS is during infancy, with only 7.5% (eight) cases having been reported in this age group. ODS has a similar predilection for both males and females. In our current review of 106 cases (Supplementary Table), gender identification was available for 104 children, of whom 49 were male and 55 were female.

Etiology

Berry and Olszewaski in 1963[7] were the first to suggest a potential role for electrolyte imbalance in the development of ODS. It

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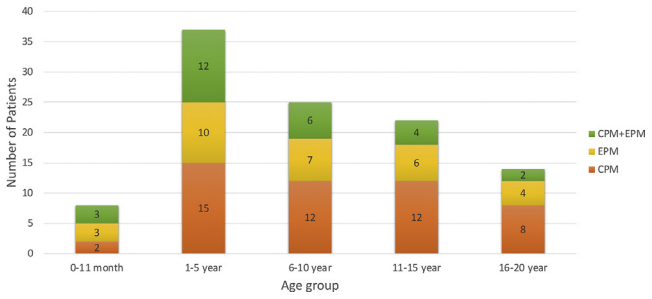

FIGURE 1. Prevalence of pediatric-onset osmotic demyelination syndrome in different age groups. CPM, central pontine myelinolysis; EPM, extrapontine myelinolysis. The color version of this figure is available in the online edition.

was only in 1980 that Leslie et al.[8] described a rapid rise in serum sodium as the cause of osmotic demyelination. ODS is usually associated with a serum sodium correction of greater than 12 mmol/L in a 24-hour period. In two studies wherein patients presented with neurological complications following a serum sodium correction by more than 12 mmol/L/day, almost 64% presented with a clinicopathological diagnosis of CPM.[9,10] ODS following rapid serum sodium correction is mostly seen in patients with chronic hyponatremia. In patients with only a few hours of acute hyponatremia (e.g., marathon runners and drug abusers), rapid serum sodium correction usually does not induce ODS.

Lampl and Yazdi 2002[11] noted that ODS is most commonly associated with chronic alcoholism (39%), followed by rapid correction of hyponatremia (21.5%) and liver transplantation (17.4%). Less commonly, ODS has been associated with electrolyte disturbance such as hypernatremia,[12,13] hypokalemia,[14-18] and hypophosphatemia[19-21]; renal failure; hemodialysis[22,23]; refeeding syndrome; anorexia nervosa[24]; diabetes mellitus[25]; leukemia[26]; lymphoma[27]; acquired immunodeficiency syndrome[28]; Wilson disease[29]; systemic lupus erythematosus[30]; Sjögren syndrome[16]; and burns.[13] In our review of the literature, ODS in children was noted following correction of hyponatremia in 30 cases and hypernatremia in 15 cases.

Pathogenesis

Osmotic myelinolysis is usually seen in areas of the brain with a maximum admixture of gray and white matter as seen in the central pons and other central nervous system regions of EPM.[31] In the central pons, the transverse pontocerebellar fibers[32] are most frequently involved, followed by long rostrocaudal tracts with relative sparing of neurons and axons.

Disruption of the blood-brain barrier (BBB) is thought to have an important role in the pathogenesis of ODS. Rapid correction of hyponatremia or an increase in serum sodium causes water to move into the extracellular space, causing shrinking and dehydration of brain vascular endothelial cells and glial cells, thereby causing disruption of BBB tight junctions and axonal sheer damage. Disruption of BBB allows access of cytokines, lymphocytes, complement proteins, and vasoactive amines to central nervous system tissue, possibly leading later to inflammatory demyelination.[33,34]

Gankam-Kengne et al.'s 2017 work in a rat model showed that ODS might be a consequence of proteostasis failure in severe osmotic stress. The authors observed diffuse protein aggregation and ubiquitination following rapid correction of chronic hyponatremia. During later stages of the syndrome, they found demyelination in similar areas.[35] More recent work from Bouchat et al. in 2018 has shown that regional astrocyte and oligodendrocyte loss precedes ODS. The authors noted the increased expression of interleukin-1β messenger RNA (mRNA) and tumor necrosis factor-α mRNA during ODS in mice. These cytokines are secreted from activated microglial cells or damaged astrocytes during injury, which later leads to BBB disruption, compromises oligodendrocyte survival, and causes neuroinflammation.[36]

The pathophysiology of ODS is potentially multifactorial and may differ depending on the underlying etiology. For instance, hyperammonemia (without sodium dysregulation) induces ODS and may not share similar pathophysiology as seen with rapid sodium correction. Molecular weight of ammonia is only 17.03 g/mol and is therefore not osmotically active. Ammonia causes upregulation of aquaporin-4 in astrocytes, which causes astrocyte swelling.[37] Rapid correction of hyperammonemia may induce aquaporin-4 dysregulation (as seen with chronic neuroinflammatory diseases, i.e., neuromyelitis optica and multiple sclerosis) causing osmotic stress and thus ODS.

Histopathological images from patients with ODS may show intramyelinic splitting, vacuolization, and rupture of myelin sheets. During the acute stage of ODS, a large number of macrophages with no lymphocytes and moderate astrocytosis can be seen.[38]

Clinical presentation

The clinical syndrome is usually seen several days after a rapid rise in serum sodium (more than 12 mmol/L/24 hour) or osmotic imbalance from other electrolytes. Rare cases with slow serum sodium correlation have also been reported. Before presenting the symptoms of ODS, patients may have neurological symptoms of encephalopathy. These symptoms may correct following initial correction of electrolytes. In the next few days (usually two to six days), patients may then present with new symptoms secondary to ODS.[39]

Clinically, ODS may present with a wide range of symptoms, including progressive spastic quadriparesis, pseudobulbar palsy, pseudobulbar affect, dysarthria, dysphagia, ophthalmoplegia, ataxia, nystagmus, and cranial nerve palsies. Severe cases may present as “locked-in” syndrome or death.[40,41]

Extrapontine myelinolysis presentation depends on the location of the lesion. EPM may present as altered mental status, seizures, emotional lability (uncontrollable episodes of crying), akinetic mutism, pure word deafness, gait disturbance, myoclonus, parkinsonism, dystonia, or reappearance of snout, grasp, or rooting reflexes. Rare examples of cervical and thoracic osmotic demyelination have also been documented; these individuals typically present with loss of pain perception and motor weakness.[12,39,42-46]

Radiology

Magnetic resonance imaging (MRI) of the brain (and spine) is the diagnostic modality of choice to demonstrate CPM and EPM. Sequential MRIs of the brain are frequently performed over a period of weeks to months to examine the progression or regression of the lesion depending on clinical symptoms.

CPM on MRI is seen as T2 hyperintensity in the central pons, with sparing of the ventrolateral pons, tegmentum, and corticospinal tracts, which produces a characteristic trident-shaped, bat-winged, or piglet appearance (Fig 2A). The lesion is hypointense on T1 with no mass effect. Contrast enhancement is usually not seen, but if present, it is noted mostly in border regions. Pontine lesions are usually symmetrical, but asymmetrical unilateral lesions have been reported.[12] Extrapontine lesions are usually bilateral and most commonly noted over cerebellar peduncles, globus pallidus, thalamus, lateral geniculate body, putamen, external and extreme capsule, splenium of corpus callosum, and supratentorial white

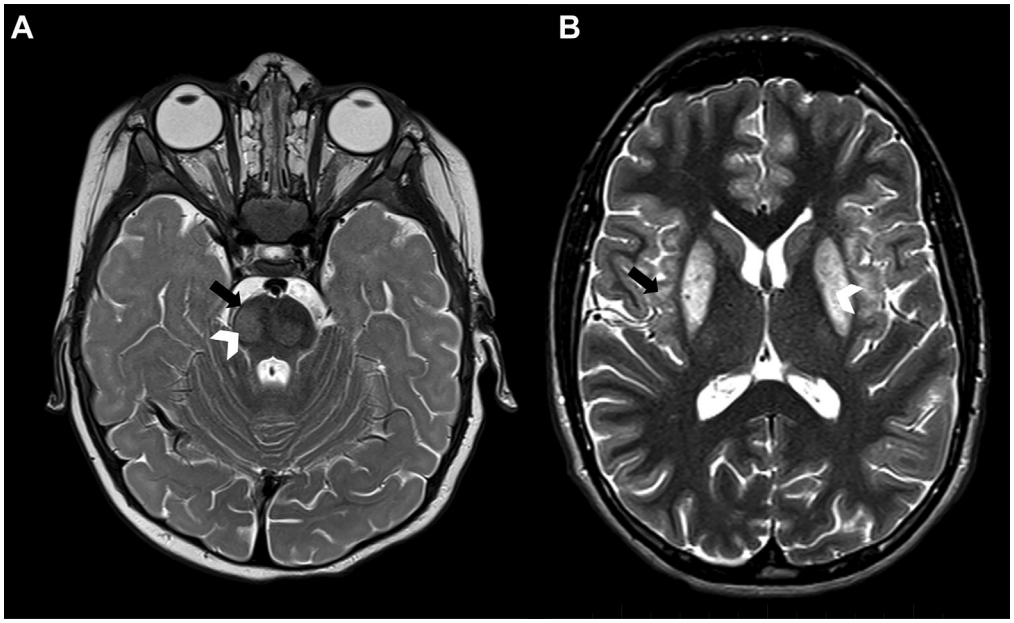

FIGURE 2. Axial T2-weighted magnetic resonance image of the brain demonstrating (A) T2 signal hyperintensity within the central pons (arrowhead) with relative sparing of the periphery (arrow) characteristic of central pontine myelinolysis and (B) T2 signal hyperintensity involving the basal ganglia including pronounced involvement of both putamen (arrowhead) and insula (arrow) characteristic of extrapontine myelinolysis.

matter (Fig 2B).[47] Rarely, involvement of the hippocampus and amygdala has also been reported.[48,49]

Diffusion-weighted image sequence on MRI in patients with ODS usually shows hyperintense pontine and extrapontine lesions, whereas apparent diffusion coefficient (ADC) may be low, normal, or slightly elevated. A decrease in ADC early in the disease usually suggests an underlying cytotoxic edema.[50,51] A normal ADC with increased signal on T2-weighted images has been associated with good recovery and prognosis.[52,53] ADC also may help differentiate ODS from other conditions (e.g., tumors, acute disseminated encephalitis, and multiple sclerosis), which may mimic ODS with similar clinical symptoms. Another differential consideration includes infarction, but unlike these previously mentioned conditions, which usually have high ADC values, recent infarction will demonstrate low ADC values.

Extrapontine lesions rarely resolve completely. Even if patients make a good clinical recovery,[54] lesions usually persist on MRI. A delayed increase in T1 signal has been reported due to possible deposition of iron or other minerals.[55-57]

Magnetic resonance spectroscopy is now increasingly used in the diagnosis of ODS.[49] Low choline (Cho), *N*-acetylaspartate, and lipid levels with an increased Cho-creatine ratio are seen with ODS, suggesting an increased neuronal loss and gliosis.[58-60] Magnetic resonance spectroscopy can also help differentiate EPM lesions from other disorders such as primary central nervous system lymphoma, which gives similar symmetrical bilateral basal ganglion lesions. Lymphomas usually show increase lipid, high Cho peak, and low *N*-acetylaspartate levels.[58]

Diffusion tensor imaging and fiber tracking can be used for prognostication in ODS. Conventional T2-hyperintense magnetic resonance images are not capable of discriminating demyelinating diseases from axonal loss.[61,62] Diffusion tensor images can be processed to achieve fractional anisotropy (FA) and mean diffusivity (MD) values. Both FA and MD help differentiate cytotoxic from vasogenic edema and assess if there is a loss of fiber tracts. Decreased FA and increased MD values are typically seen with demyelination, gliosis, and associated fiber loss (Fig 3).[63]

Positron emission tomography has also been used in the diagnosis of ODS. A few reports describing the use of 18F-fluorodeoxyglucose have shown an increased uptake during active ODS. It is hypothesized that the increased uptake is due to increased metabolism of glial cells, macrophages, and activated astrocytes.[64,65]

Outcome

In the review of 106 pediatric ODS cases, treatment response was available in 102 cases. In two subjects, ODS was identified incidentally (asymptomatic presentation), whereas in the other two cases outcomes were not listed. In this cohort of 102 subjects, 39 (38%) had a complete recovery, 23 (22%) had partial recovery, and 40 (39%) subjects died within weeks to months of onset of ODS symptoms. As most of the mortalities occurred in the twentieth century, an overall improved outcome was noted when patients from that era were excluded. In patients presenting with ODS after the year 2000, treatment response was available for 45 subjects, and of them, 27 (60%) had a complete recovery, 14 (31%) had partial recovery, and only four (9%) died (Fig 4). This improved outcome is likely due to the increased use of MRI of the brain leading to early detection of signatures consistent with ODS and a subsequent increase in the diagnosis of the milder or asymptomatic form of the disease.

Prognosis

Severe hyponatremia (less than 115 mEq/L), associated hypokalemia, or low Glasgow Coma Scale score (less than 10) at presentation or ODS following liver transplant are reported to be poor prognostic factors in ODS.[4,66] A normal ADC on MRI of the brain with increased signal on T2-weighted images is associated with a good prognosis.[52] The anatomic location and size of the demyelinating lesion are usually not associated with outcome (Fig 4).[67] Patients with large lesions can make a complete neurological recovery over the course of weeks or months.

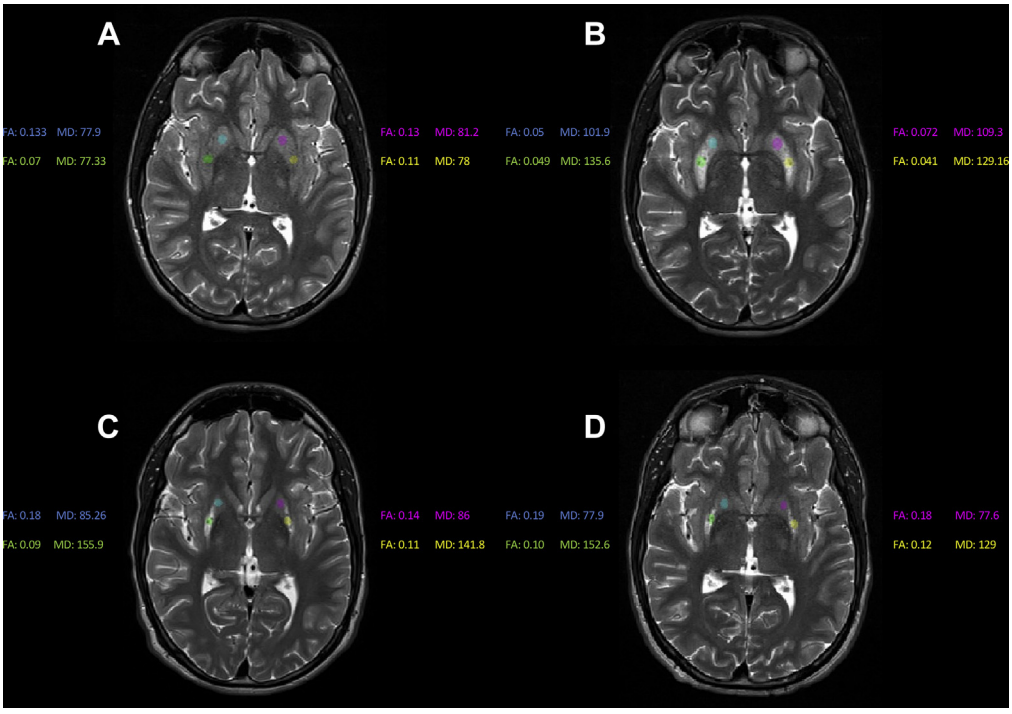

FIGURE 3. T2-weighted axial magnetic resonance images of a 17-year-old male with extrapontine myelinolysis performed at (A) 1 week, (B) 3 weeks, (C) 15 months, and (D) 18 months following onset of his clinical symptoms. Progression of T2 hyperintensity with the appearance of cystic encephalomalacia is noted over bilateral posterior putamen. Fractional anisotropy (FA, 10^{-3} mm^2/s) and mean diffusivity (MD, 10^{-5} mm^2/s) values obtained from spherical locations (size 120 mm^3) are shown. An early marked decrease in FA (posterior greater than anterior) and a progressive increase in MD (posteriorly) are noted suggesting fiber loss and gliosis. The color version of this figure is available in the online edition.

Management

No effective treatment has been defined for ODS. Current management consists of general supportive care. Electrolyte imbalance (hyponatremia, hypernatremia, hypokalemia, hypophosphatemia, and hyperammonemia), if found, should be corrected slowly, although there are reports of ODS even after slow electrolyte (sodium) correction.[68] According to US guidelines, hyponatremia should be corrected at the rate of 10 to 12 mmol/L/day or by 8 mmol/L/day in high-risk cases (hypokalemia, alcoholism, malnutrition, or liver disease).[69] Ironically, the goal of current electrolyte management is to prevent ODS from occurring, and there are no specific interventions or guidelines once ODS has already occurred. Rapid reinduction of hyponatremia has been proposed as a potential therapeutic maneuver.[70] In rat models, rapid reinduction of hyponatremia after initial excessive sodium correction has been shown to reverse the pathological process of demyelination and prevent subsequent brain damage. There are no clinical trials in humans to test this hypothesis, although two case reports in adults with ODS describe relowering of serum sodium with reversal of symptoms and favorable neurological outcome.[68,71]

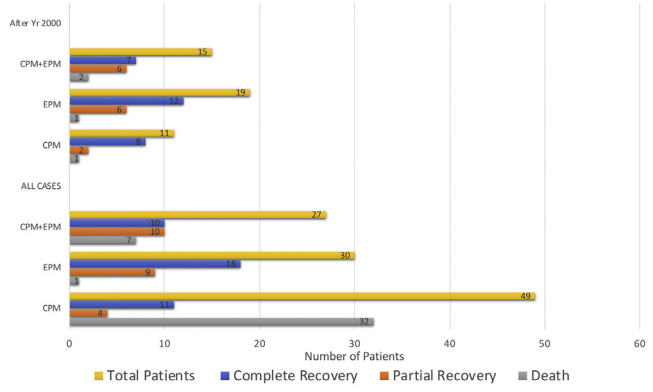

FIGURE 4. Outcome of osmotic demyelination syndrome in children. CPM, central pontine myelinolysis; EPM, extrapontine myelinolysis. The color version of this figure is available in the online edition.

Potential benefit of steroids has been described in adults and children with ODS. In our review of cases, nine children with ODS were treated with steroids alone (prednisolone, dexamethasone, methylprednisolone) in various dosages (Supplementary Table).[12,72-79] Of them, six had complete neurological recovery, one had partial recovery, and two died. Two other children received steroids along with intravenous immunoglobulin (IVIG),[80] and, of them, one had complete recovery and the other had partial recovery. In the review of cases since the year 2000, seven of eight patients who received steroids (alone or in combination) achieved complete neurological recovery. These subjects were of different age groups and had different etiologies for their ODS (hyponatremia, hypernatremia, anorexia, hyperammonemia, carbamate poisoning, and idiopathic). In the nonsteroid group of 37 subjects, only 20 patients had a complete recovery. This finding suggests that regardless of age and etiology, steroids may have a potential therapeutic effect in children when used early in the course of the illness along with supportive care.

IVIG and plasmapheresis have also been used in limited cases after the development of ODS, with some positive results. Most of the cases described are in adults.[81] In the review of the literature, IVIG was used in four subjects[19,80,81] (two children and two young adults). Two of them received only IVIG,[80] and the other two received IVIG in combination with steroids.[19,82] Of these patients, three achieved full neurological recovery, suggesting that IVIG may have potential for benefit. Recent work from Bouchat et al. in 2018

supports our hypothesis that immune modulators may be beneficial, as activated microglia and damaged astrocytes play an initial and major role in ODS development.[36] Use of steroid and IVIG early in the course of the illness may modulate microglia response and thus prevent a cascade of apoptosis, neuroinflammation, and demyelination.

Other potential treatments investigated for ODS include the use of thyroid-releasing hormone (TRH), myoinositol, lovastatin, and minocycline.[83-86] Most of these treatment modalities are investigated in rat models; human clinical trials are lacking. Use of TRH has been documented in two people (CPM and EPM, respectively), and both individuals exhibited marked improvement of their neurological symptoms. The mechanism of TRH is unknown, but it may be related to increased cerebral blood flow and L-dopa.[83,87,88] Neuroinflammation (tumor necrosis factor-α and interleukin-1β) can have a toxic effect on dopaminergic neurons, thereby causing depletion of intracerebral levodopa.[89] L-Dopa crosses the BBB, replenishes depleted intracerebral levodopa, and helps resolve neurological symptoms resulting from the depletion.

Conclusion

ODS is uncommon in children, is multifactorial, and has no gender preponderance. The highest prevalence of ODS is noted between the ages one and five years, and the prevalence declines with increasing age. The outcome of ODS in children is generally favorable, with 60% achieving complete neurological recovery. Our review of the literature suggests a potential benefit of steroids and IVIG in ODS, although additional controlled studies are lacking.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2019.03.018.

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