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REVIEW ARTICLE

Central pontine myelinolysis and the osmotic demyelination syndromes: an open and shut case?

Pyari Bose[1]

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Abstract

Central pontine myelinolysis and extrapontine myelinolysis are collectively called the osmotic demyelination syndromes. Despite being described in 1959, there are several aspects of the disorder that remain an enigma. Animal models and neuroimaging techniques have allowed us to understand the condition better. From being a universally fatal disorder that was diagnosed post mortem, increased awareness, neuroimaging techniques and supportive care have enabled us to make the diagnosis ante-mortem. This has also led to a significant drop in associated mortality. The aim of this review is to highlight the clinical spectrum, neuroimaging findings, and recent developments.

Introduction

Adams et al., first described central pontine myelinolysis as a clinicopathological entity in 1959. Several outstanding reviews have been published subsequently on the disorder over the years. Although some authors call the spectrum of both central pontine myelinolysis and extra pontine myelinolysis collectively as osmotic demyelination syndromes, the original authors were very clear in their paper why they wanted to avoid the term demyelination. Adams et al., reasoned that in this hitherto peculiar disorder, the myelin loss was not associated with inflammation. They wanted to differentiate the pathology of this condition from multiple sclerosis and other neuroinflammatory disorders in which myelin loss was associated with inflammation. When they described the condition, the authors hypothesised the underlying cause to be either a toxin related or due to a nutritional deficiency [1]. For the purpose of this review and to avoid confusion, the author uses the terminology 'osmotic demyelination syndrome' (ODS) in relevant sections when there is need to encompass both central pontine and extrapontine myelinolysis.

✉ Pyari Bose
pyaribose@gmail.com

[1] Department of Neurology, Auckland City Hospital, Auckland, New Zealand

Clinical presentation

With key developments since the original description, it has become clear that there is no classical presentation of osmotic demyelination syndromes. The presentation is multifaceted and diverse. It is important for the clinician to be aware of the distinct clinical presentations.

Asymptomatic

Since the original description of cases, it is now known from autopsy findings and clinical cases, that many are asymptomatic [2–4]. Asymptomatic central pontine myelinolysis was found in 21 out of 220 autopsies of consecutive patients with chronic liver disease [5]. A 12-year retrospective analysis involving review at autopsies of 3247 brains, revealed 15 cases of central pontine myelinolysis. This analysis suggested an overall incidence of 0.5% of the cases, emphasising that a large proportion of cases maybe asymptomatic if not the majority [6]. It remains to be seen whether asymptomatic cases represent a different pathophysiological mechanism as opposed to the vast majority of symptomatic cases that appear to be iatrogenic. The difference in prognosis between asymptomatic and iatrogenic cases is not known.

Acute encephalopathy

An initial encephalopathic stage is described in several cases of iatrogenic osmotic demyelination syndromes during electrolyte shifts.

Flaccid quadriparesis or quadriplegia

This phase is usually seen within the first 5 days of onset of symptoms. An initial phase of flaccid quadriparesis along with dysarthria and dysphagia can be seen. During this phase, the patient may be able to moves their eyes to command, suggestive of a 'locked-in' state. This is thought to be due to abrupt disruption of the corticospinal tracts and spinal shock. A lesion in the pons can explain these clinical features [1, 7].

Spastic quadriparesis or quadriplegia

By about the fifth day from the onset of symptoms, once the disruption in the corticospinal tracts gets firmly established, upper motor neuron signs may become prominent. The patient may have increased tone, brisk reflexes, clonus and positive Babinski sign [1, 7].

Pseudobulbar effect

Due to disruption of corticobulbar tracts within the pons, the patient may have difficulty with speech and swallowing [1].

Movement disorders

Various movement disorders are being increasingly being reported with osmotic demyelination syndromes especially when there is extrapontine myelinolysis. Due to basal ganglia involvement, symptoms like tremor, chorea, dystonia, ataxia, mutism and catatonia have been reported. Involuntary slow writhing and jerking movements of the anterior abdominal wall (known as belly dancer's syndrome) occurring in conjunction with osmotic demyelination syndrome has also been reported (see Fig. 3) [8–10].

Death

When the syndrome was first described, the fatality was total and the cases all being diagnosed post-mortem. Death was reported usually by around day 13 following onset of symptoms. However, with improved awareness, intensive care access and neuroimaging, cases are now mostly detected antemortem and there has been a dramatic decline in mortality. This will be further discussed in the section on prognosis.

The 'plastic revolution'

Since the description of cases by Adams et al., in their seminal paper published in 1959, there was been an explosion in cases reported worldwide [11, 12]. The location of the lesions is such that, it could not have been missed by pathologists had it occurred more frequently prior to 1959. It is thought that the increase in cases worldwide were down to the rampant use of intravenous fluids at the time, the so called 'plastic revolution.' The routine availability of serum electrolyte measurements may have also played a part. With the availability of this, sustained therapeutic interventions by clinicians to 'normalise' sodium levels using intravenous fluids may have contributed to the increased incidence of myelinolysis [8, 13, 14]. The author would like to coin this the 'restless electrolyte correction syndrome' amongst clinicians when there maybe the urge to correct electrolyte levels in situations where this may not be necessary.

Risk factors

Chronic alcoholism

Chronic alcoholism has consistently featured in association with osmotic demyelination syndromes in up to 40 percent of cases reported [8, 15]. The exact mechanism through which chronic alcoholism contributes to the syndrome remains to be elucidated. Possible explanations include disruption of sodium regulation, malnutrition, advent of hepatic cirrhosis and dysregulation of antidiuretic hormone (ADH) [8, 15].

Malnutrition

Malnutrition has also been commonly reported in association with central pontine myelinolysis, usually in conjunction with chronic alcoholism. The presence of Marchiafava-Bignami disease and Wernicke-Korsakoff syndrome in in up to 30% of autopsy specimens of patients with osmotic demyelination disorders suggests that nutritional deficiencies especially thiamine deficiency may have a role in the development of osmotic demyelination disorders. Adams et al., speculated a nutritional deficiency as the most likely cause for this disorder as their four canonical cases had underlying chronic alcoholism or malnutrition [1, 8].

Hyponatremia

The association between rapid rises in serum sodium from baseline hyponatremia as a causative factor for central pontine myelinolysis was suggested by Norenberg et al. [16]. Subsequently, rapid correction of hyponatremia leading to experimentally induced central pontine myelinolysis was shown in an animal study involving 60 dogs. The dogs were rendered hyponatraemic by the administration of intramuscular vasopressin (antidiuretic hormone) and intraperitoneal administration of 2 litres of water. Amongst the animals that survived the sustained hyponatremia for at least 4 days, they were divided into four groups A, B, C and D based on the

intervention carried out (i.e., uncorrected hyponatremia, hypertonic saline infusion in normal dogs, hyponatremia treated with water restriction and hyponatremia treated with hypertonic saline, respectively). Following autopsy, 50% (5/10) dogs with hyponatremia who underwent correction with hypertonic saline (Group D), were found to have autopsy findings consistent with myelinolysis [14].

A retrospective analysis of 1490 patients admitted with sodium of less than < 120 mEq/L underwent rapid correction in around 41% of the cases. The authors defined rapid correction as an increase of sodium by more than 8 mEq/L in a 24-h period. Amongst the patients who underwent rapid correction, approximately 1% developed osmotic demyelination syndrome [17].

Liver transplantation

Liver transplantation constitutes around 17% of cases reported of osmotic demyelination disorders since 1986. In a study involving 1730 consecutive liver transplant patients, about 8% had radiological documented central nervous system lesions consistent with central pontine myelinolysis [18].

Hypokalaemia

Hypokalaemia has been reported in association with osmotic demyelination syndromes. The very first canonical case described by Adams et al., was found to have hypokalaemia [14]. Several cases have been reported in literature since [7, 19, 20]. Association with hypokalaemia was also suggested in a literature review of osmotic demyelination syndrome. Out of 74 cases in which both serum potassium and sodium were measured at presentation, 89% of cases had documented hypokalaemia. The sodium pump (Na–K-ATPase) located in the cell membrane is responsible for transporting potassium into cells by exchanging sodium and is integral in regulation of cell volume. Reduced Na–K-ATPase activity during hypokalaemia may impact the ability of the cell membrane to preserve its volume against rapid changes in osmolality during correction of hyponatremia. This may lead to cell shrinkage and apoptosis. Hence there is a case for concurrent measurement and correction of electrolytes to reduce the impact of osmotic demyelination [7, 21].

Refeeding syndrome

Several clinical complications can occur during aggressive nutritional correction in malnourished patients due to rapid fluid and electrolyte shifts. This is collectively called refeeding syndrome. Deficiencies maybe seen in phosphate, magnesium, glucose, vitamins (especially thiamine) and sodium. Trying to replete the deficiencies quickly can be complicated by congestive heart failure, pulmonary oedema, cardiac arrhythmias, seizures and death [22, 23]. Osmotic demyelination syndrome has been reported in the context of refeeding syndrome [7, 24]. With rapid gradient shifts in osmoles associated with both refeeding syndrome and osmotic demyelination disorders, it remains to be seen whether osmotic demyelination syndrome is a central nervous system manifestation of refeeding syndrome [25]. Rapid electrolyte shifts may place a severe strain on the energy deprived glial cells in the brain. This can set off a cascade leading to glutamate receptor stimulation, opening up calcium channels, mitochondrial permeability and ultimately initiate apoptosis [26].

Others

Osmotic demyelination syndrome has also been reported in the context of burns. In a study of 139 burns patients that underwent autopsy over a 17-year period, 7% ($n = 10$) were found to have findings consistent with central pontine myelinolysis [27]. It has also been reported in hyperemesis gravidarum [12]. The syndrome has also been reported in the contexts of rapid shifts in serum glucose [28–30]. Other less common conditions in which osmotic demyelination disorders have been reported include autoimmune disorders (Sjögren's syndrome and systemic lupus erythematosus), HIV, acute intermittent porphyria, anaphylactic shock and cytomegalovirus hepatitis, brain tumours, Hodgkin's disease, craniopharyngioma, renal disease, sepsis, Wilson's disease, sickle cell disease, adrenal insufficiency, congestive heart failure, liver failure and chemotherapy [15, 26].

Pathogenesis

The exact mechanisms involved in causing osmotic demyelination syndromes in not known. Serum sodium is a key determinant of effective serum osmolality. Though the initial connection with electrolyte disturbances is usually attributed to Finlayson [31] or Tomlinson [32], it was Norenberg and colleagues who showed the association with hyponatremia using compelling evidence from a case series of 12 patients [16]. Laureno was successful in experimentally inducing myelinolysis using animal models that established rapid correction of hyponatremia as a key causative factor [14].

Osmolality is the concentration of a solution in terms of osmoles of solute per kilogram of solvent. Hence plasma osmolality alludes to the quantity of solute that is dissolved in 1 kilogram of plasma. Serum sodium is a key determinant of effective serum osmolality. In the equilibrium state, extracellular osmolality and intracellular osmolality remains the same. There is null net movement across the cell membrane. When serum sodium concentration drops,

extracellular osmolality reduces as a result. As a consequence, water moves from the extracellular space into the intracellular compartment. Hence hypotonicity can cause the cell to swell and hypertonicity will lead to cell shrinkage as water moves from inside to outside. The development of symptoms will depend on the speed at which the change occurs and whether these overwhelm the brain's adaptive mechanisms. One of the earliest defence mechanisms of the brain against hypotonicity that comes into play, is the shift of interstitial sodium rich fluid from the brain parenchyma, to the cerebrospinal fluid (CSF) and subsequently to systemic circulation through hydrostatic pressure. This measure serves to protect the brain from rapid oedema. Within the first hours of resultant hyponatremia, there is a significant decrease in the intracellular content of sodium, chloride, and potassium [8, 33].

As a late mechanism of brain adaptation to chronic hyponatremia, it has been shown in a rat model that after 4 days, brain electrolyte content reduced by 33%, 11%, and 17% for chloride, sodium, and potassium, respectively. However, the brain water content only increased by 0.6% [33, 34]. The loss of organic osmoles like myoinisotol, taurine and glutamate over the next day to the next few days, renders the cell isotonic compared to extracellular space and ensures maintenance of cell volume [8].

It is thought that rapid correction of established hyponatremia may disrupt the blood brain barrier, leading to accumulation of cytokines and complement factors. In experimental models, the astrocytes and oligodendroglia seem particularly susceptible to the osmotic stress [35].

These pathophysiological mechanisms provide an explanation for osmotic demyelination syndromes in the context of rapid correction of hyponatremia. However, the occurrence of the disorder in conditions where the serum sodium is normal suggest other important yet unknown mechanisms maybe at play.

Imaging

Conventional imaging (CT and MRI) may lag behind clinical manifestations but have allowed ante-mortem diagnosis and management of osmotic demyelination disorders. Though CT is less sensitive than MRI imaging in detecting early changes, occasionally a reduced attenuation within the pons may be seen (see Fig. 1) [7]. MRI imaging may show a symmetric signal intensity abnormality in the central pons with T2-weighted and FLAIR imaging (see Fig. 3). Early diagnosis of central pontine myelinolysis may be made with diffusion-weighted imaging (DWI) [36]. In a study looking at the outcome of patients with central pontine and extra pontine myelinolysis ($n=44$) magnetic resonance imaging findings offered no prognostic significance. The extent of

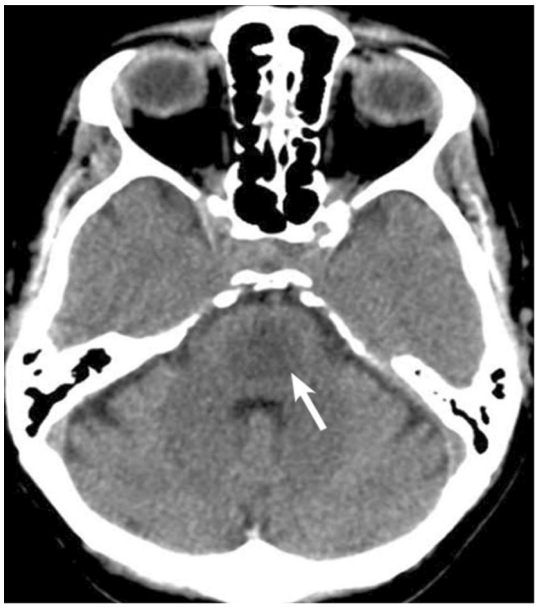

Fig. 1 Computerised tomography (CT) scan of head. A large area of reduced attenuation centrally within the pons raising the possibility of central pontine myelinolysis. An MRI scan was subsequently arranged for confirmation (see Fig. 2) [7]

the pontine lesions seen on the scans did not co-relate with the severity of clinical findings during the acute phase of disease. Neither did the persistence of the pontine lesions seen on magnetic resonance imaging correlate with clinical improvement [37]. Another aspect worth stressing is that not all pontine lesions seen by neuroimaging represents central pontine myelinolysis and taking a clinical history is paramount [38]. Functional imaging studies in central pontine myelinolysis have shown hypermetabolism in the brainstem [26]. Fluorine-18-fuorodeoxyglucose (F-18-FDG) positron emission tomography/computed tomography (PET/CT) has shown showed localized uptake in the pons consistent with magnetic resonance imaging findings [39, 40]. Functional imaging may provide a vital role in the diagnosis and monitoring of patients with osmotic demyelination syndromes in the future (Fig. 4). These modalities need further investigation.

Histopathology

Autopsy findings show that central pontine myelinolysis predominantly involves the basis pontis. Histology shows evidence of demyelination, with sections stained for myelin usually showing a sharply demarcated pallor in the centre of basis pontis. The original authors described the loss of oligodendrocytes with sparing of axons and nerve cells except at the very center. Inflammation was absent [1, 2, 15]. Within a few years following the description of central

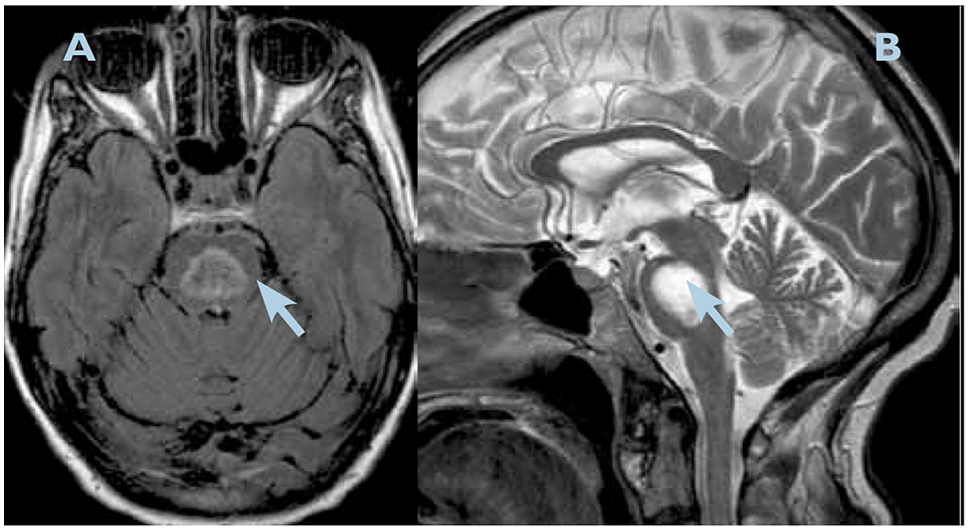

Fig. 2 **a**, **b** Magnetic resonance imaging (MRI) Brain scans confirming the diagnosis of central pontine myelinolysis showing the increased T2 weighted signal in the central pons [7]

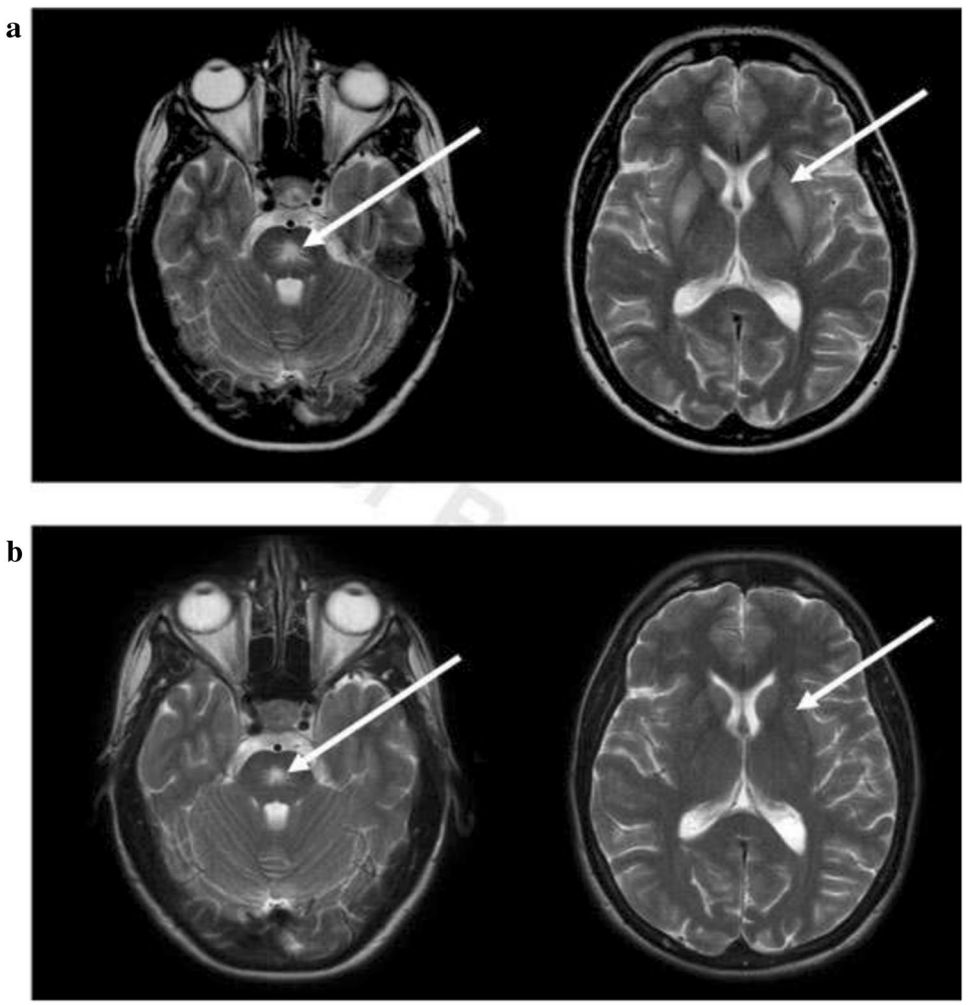

Fig. 3 A case of Belly Dancer's Syndrome Following Central Pontine and Extrapontine Myelinolysis. T2-weighted MRI Brain scans obtained 1 day after symptom onset (**a**) showed characteristic bilateral hyperintensities in the central pons (left panel) as well as bilaterally in the caudate nucleus and the putamen (right panel). The follow-up T2-weighted MRI scan 5 months later (**b**) demonstrated unchanged pontine signal alterations (left panel) but incomplete disappearance of basal ganglia lesions (right panel). Abnormal hyperintensities indicated by arrows [9]

pontine myelinolysis, it became apparent that similar lesions could also involve extrapontine sites like cerebellum, lateral geniculate body, external capsules, hippocampus, putamen, thalamus and caudate nucleus. Unusual sites include spinal cord, mamillary bodies, amygdala and subthalamic nucleus [15]. Subsequent animal models have undergone detailed

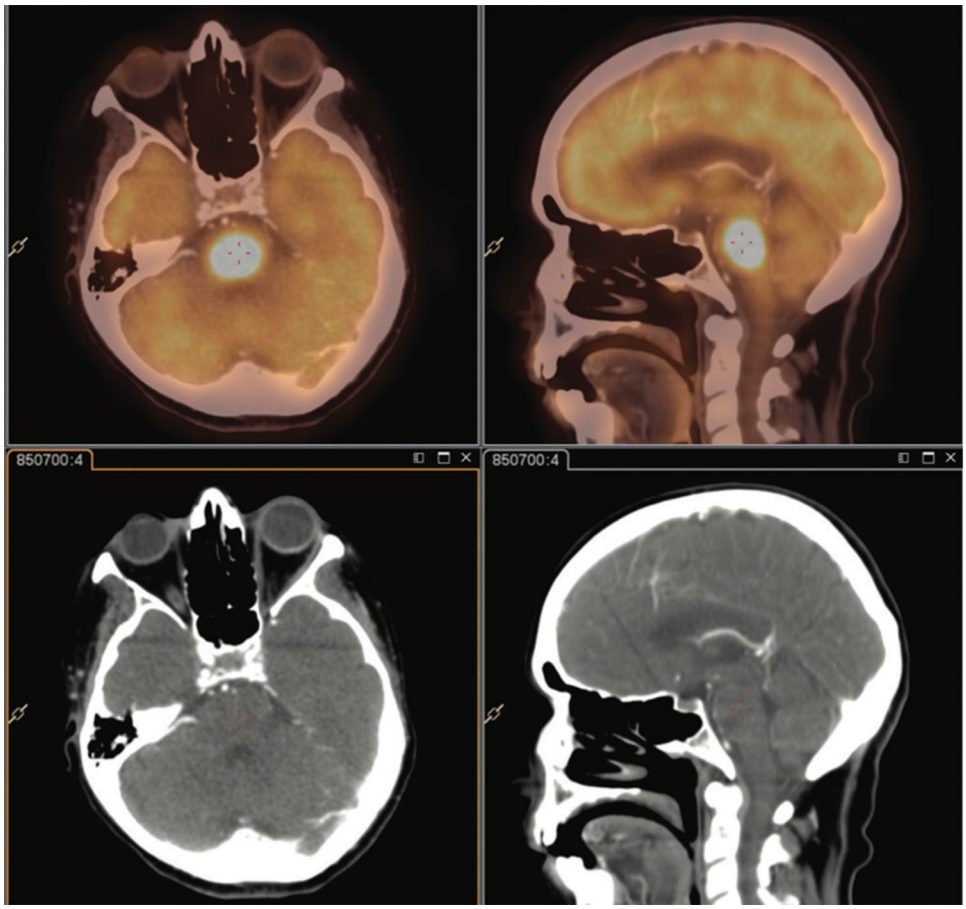

Fig. 4. 18F-FDG PET/CT scan of a 51-year-old Caucasian female with symptoms of central pontine myelinolysis. Scan shows localized FDG uptake in the pons, with normal and symmetrical activity in the rest of the brain [40]. (Creative Commons Attribution-Non Commercial-ShareAlike License (CC BY-NC-SA))

microscopic evaluations and the findings are similar to autopsy findings in humans. Animal models have shown early opening of the blood brain barrier which may constitute the initial injury. Animal models have also suggested that microglial activity and consequent release of cytokines may accentuate myelin destruction [15]. See Fig. 5 for histopathology findings in a case of chronic asymptomatic central pontine myelinolysis with histological evidence of remyelination.

Why the pons and the extrapontine regions?

Ever since the first description of the condition, scientists have found it very intriguing and peculiar, the distribution and localisation of the lesions. Several explanations have been put forward to explain this. One theory suggests the 'grid' like intertwining longitudinal and transverse fibres within the pontine basis is prone to myelinolysis when oedematous. This arrangement may severely impact mechanical flexibility during osmotic stress [13]. Another proposed hypothesis based on a rat model is the blood–brain barrier breakdown which results in oedema within the highly vascular gray matter regions involved. The resultant oedema could damage the neighbouring white matter tracts [41–44]. The vascular supply to the central pons may also be a crucial factor. The perforating branches of the basilar artery supplies the region. These vessels have a low pressure differential and leading to poor perfusion of the central pons which may be exacerbated by any metabolic rearrangements [26]. These hypotheses do not take into account the extrapontine involvement. The localisation and activity of Na+/K+-ATPase pump activity, the role of glutamate and other excitatory molecules in the context of osmotic stress needs to be explored further to clarify whether these mechanisms provide the ultimate induction to apoptotic cell death in osmotic demyelination syndromes [15, 26]. Functional imaging studies may provide more clues in the future.

Management

Most management strategies for osmotic demyelination syndromes are centred around sodium levels. In patients with established hyponatremia, cerebral adaptation during very severe hyponatremia (e.g., < 105 mEq/L) requires higher depletion of brain organic osmolytes. These organic osmolytes cannot be replenished quickly with rapid

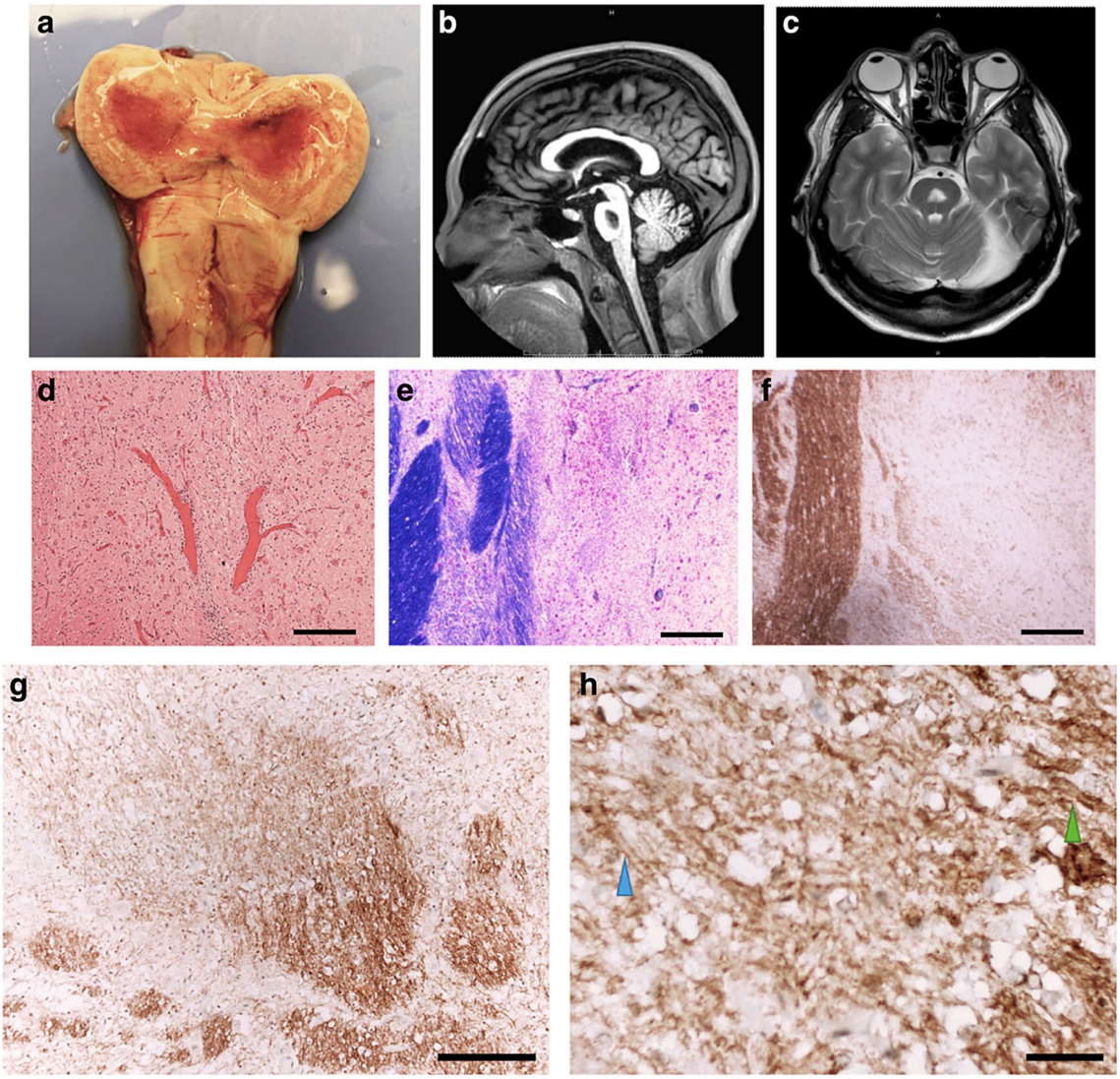

Fig. 5 **a** Post-mortem image of the fresh pons and medulla, opened sagitally from the ventral aspect. A red, central, triangular region of softening is seen with preservation of the surrounding parenchyma. **b** Sagittal T1 and **c** Axial T2 ante-mortem MRI sequences. The pons includes a trident-shaped focus of high T2 signal. Cerebellar atrophy is also noted, in keeping with the history of alcoholism. **d** Hypercellular pontine tissue, reflecting astrocytic gliosis and perivascular and parenchymal accumulation of chronic inflammatory cells (scale bar = 200 µm). **e** Staining with luxol fast blue and cresyl violet revealed a sharply demarcated region of reduced staining of myelin in the central part of the base of the pons, with good preservation of neurons (scale bar = 200 µm). **f**, **g** There was reduced labelling of myelin with anti- PLP1 in the affected region of pons (scale bar = 200 µm). **h** Included within this region were many large-calibre but thinly myelinated axons (blue arrowhead), in contrast to the normally myelinated, large-calibre fibres in the adjacent pons (green arrowhead) (scale bar = 50 µm). Reproduced with kind permission from the author. (http://creativecommons.org/licenses/by/4.0/). [2]

correction of sodium and hence patients are more likely to develop ODS after rapid correction. The management strategies can be discussed under prevention and treatment.

Prevention

In patients at risk for osmotic demyelination syndrome like chronic alcoholics, malnourished, chronic hyponatremia (when hyponatremia is present for 3 or more days) and patients with severe liver disease, rapid correction of sodium must be avoided. Unless there is a strong history to suggest water intoxication, if the duration of hyponatremia is not known, it would be best for the clinician to assume that this is chronic. The traditional consensus figure amongst neurologists is not to correct chronic hyponatremia in excess of 8 mmol/L/day. However, there are no randomized controlled trials to guide correction. These figures are largely derived from animal models and some observational studies in humans [8, 14, 15, 45]. It is important to bear in mind that meticulous correction

of hyponatremia may not stop the occurrence of osmotic demyelination disorders [15]. Factors like unrecognized hypovolemia and other reversible causes of water retention may lead to inadvertent overcorrection of sodium despite careful monitoring of sodium levels [46].

Treatment

Patients who have confirmed osmotic demyelination syndrome clinically and radiologically should have intensive supportive therapy involving various specialists. These may include neurologists, intensive care specialists, physiotherapists, speech and language therapists (SALT) and dietitians. No clinical trials exist to guide treatment once the syndrome has established. Reinduction of hyponatremia using desmopressin has led to complete recovery in some cases with complete resolution of MRI lesions in one case when initiated within 24 h of the onset of symptoms [47, 48]. There is currently no evidence in relowering sodium levels 24 h after the onset of symptoms.

Plasmapheresis has been tried in cases with reports of good outcome. It is thought that plasmapheresis may reduce high molecular myelinotoxic substances thereby contributing to clinical improvement [49, 50]. Intravenous immunoglobulins (IVIG) have also been used in osmotic demyelination syndromes with reports of good outcomes. The clinical effect of IVIG in this situation is assumed to be caused by the reduction of myelinotoxic substances and the promotion of remyelination [51–54].

Animal models suggest myoinisotol administration improves survival and reduces myelinolysis after rapid correction of chronic hyponatremia. More studies are needed to evaluate the role of myoinisotol as a potential therapeutic agent [55].

It is not possible to overemphasise the importance of good supportive care for patients with confirmed osmotic demyelination syndrome. With aggressive supportive therapy, patients may survive with minimal neurological sequelae. Potential secondary complications need to be anticipated like aspiration pneumonia and respiratory paralysis with immediate ventilatory support at the advent of respiratory failure. With good supportive care, patients can have a favourable outcome [7, 56]

Patients with history of alcoholism or malnutrition may lack sufficient reserve supply of glucose to maintain Na–K-ATPase pump activity, the primary mechanism responsible for electron transport in the brain. Subclinical thiamine deficiency may exacerbate this problem [15, 26]. Hence thiamine should be considered in patients with history of chronic alcoholism or malnutrition.

Prognosis

Prognosis used to be considered poor and universally fatal. However, since the initial description of the conditions, the prognosis has continued to improve with patient mortality of only 7% of cases from 1990 onwards according to one study. From what used to be an autopsy diagnosed disorder, modern imaging techniques have ensured that the condition can be detected and managed early. There is also increased awareness of this potential complication with electrolyte imbalances especially around sodium [11]. Improved Intensive care access and early intubation at the advent of respiratory complications including arrest may also be a key factor involved in improved prognosis with less severe residual neurological sequelae [7, 11].

Discussion

Hyponatremia is seen in association with osmotic demyelination disorders in up to 40% of cases but it is not a universal finding in osmotic demyelination syndromes. The occurrence of the condition in other situations where serum sodium is normal, suggests that there are still further underdetermined aspects regarding the condition apart from rapid correction of hyponatremia. Focussing solely on serum sodium may mean neglecting the other 60% of situations where sodium may not play a predominant role in the development of the condition. It is likely that the etiology of osmotic demyelination syndrome is multifactorial and linked to neuronal osmotic stress [26]. Energy deprived states like chronic alcoholism and malnutrition appear to aggravate the risk.

Conclusion

The case of central pontine myelinolysis and other osmotic demyelination syndromes, is by no means open and shut. Improved awareness and supportive care has led to a dramatic shift in the prognosis with a sustained improvement in mortality figures over the years.

Key points

1. Resist the urge to treat chronic hyponatremia

2. Anticipate osmotic demyelination syndrome in patients with risk factors like chronic alcoholism, malnutrition and those undergoing rapid osmotic shifts.
3. Once osmotic demyelination has occurred, consider reinduction of hyponatremia if within 24 h. Beyond 24 h, plasmapheresis and IVIG can be considered.
4. Consider thiamine in all patients with history of alcoholism and malnutrition.
5. Consider a multidisciplinary team approach with neurologist, intensivist, physiotherapist, dietitian, speech and language therapist.

Compliance with ethical standards

Conflicts of interest No conflict of interest.

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