

CENTRAL PONTINE AND EXTRA-PONTINE MYELINOLYSIS: THE OSMOTIC DEMYELINATION SYNDROMES

R J Martin

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Central pontine myelinolysis (CPM) was described by Adams and colleagues in 1959 as a disease affecting alcoholics and the malnourished.¹ The concept was extended from 1962 with the recognition that lesions can occur outside the pons, so-called extrapontine myelinolysis (EPM). In 1976 a link between these disorders and the rapid correction of sodium in hyponatraemic patients was suggested, and by 1982 substantially established. In this review we discuss the clinical, pathological, and aetiological features of the disease, the dilemma facing clinicians treating patients with severe hyponatraemia, and treatment opportunities.

OSMOTIC DEMYELINATION SYNDROMES: CPM AND EPM

Clinical manifestations

Central pontine myelinolysis (CPM)

Nothing has been added to the clinical description of CPM since the original report. The patient has usually gone through a biphasic clinical course, initially encephalopathic or presenting with seizures from hyponatraemia, then recovering rapidly as normonatraemia is restored, only to deteriorate several days later. The initial signs of the CPM, which reflect this second phase, include dysarthria and dysphagia (secondary to corticobulbar fibre involvement), a flaccid quadriparesis (from corticospinal tract involvement) which later becomes spastic, all from involvement of the basis pontis (fig 1); if the lesion extends into the tegmentum of the pons pupillary, oculomotor abnormalities may occur. There may be an apparent change in conscious level reflecting the “locked-in syndrome” that a large lesion in this site is particularly liable to produce. If lesions of EPM are also present the clinical picture may be very confusing, as added to the above, or even preceding, can be a variety of apparently psychiatric and behavioural changes and movement disorders (outlined below).

To summarise: “...whenever a patient who is gravely ill with alcoholism and malnutrition or a systemic medical disease develops confusion, quadriplegia, pseudobulbar palsy, and pseudo coma (‘locked-in syndrome’) over a period of several days, one is justified in making a diagnosis of central pontine myelinolysis’.²

Extrapontine myelinolysis (EPM)

The pathological changes are identical to those of CPM. Studies show that lesions can occur with or without CPM: in a necropsy series of 58 cases isolated CPM was present in about half, CPM with EPM in about three fifths, and isolated EPM in about two fifths of cases (fig 2).³ A variety of sites may be involved (table 1). The lesions are often strikingly symmetrical. The age of lesions in the various sites in EPM is contemporaneous. CPM and EPM are the same disease, sharing the same pathology, associations, and time course but differing in clinical manifestations.

Movement disorders in EPM

While no significant advance on the description of the clinical features of CPM has been made since the original report, the manifestations of EPM continue to attract publication, especially in the movement disorder literature. This is a consequence of the widespread nature of such lesions.

Mutism, parkinsonism, dystonia, and catatonia have all been described. Catatonia has been reported on a couple of occasions, once as a brief episode lasting days before resolving and being replaced with parkinsonian features, and once following the resolution of spastic tetraparesis, itself settling spontaneously over two weeks. However, this manifestation may be under-recognised. In EPM a variety of clinical features can be seen to evolve—for example, a patient who progressed from spastic paraparesis with postural limb tremor and myoclonic jerks to a parkinsonian picture with choreoathetosis, and finally into a permanent parkinsonian state with dystonia. In another case parkinsonism dominated the clinical picture with signs of pyramidal dysfunction. These then resolved over four months, being replaced by transient retrocollis and oromandibular dystonia and a permanent focal dystonia of the arm with spasmodic dysphonia.

Correspondence to:
Dr R J Martin, Department of
Neurology, Gloucestershire
Royal Hospital, Great Western
Road, Gloucester GL1 3NN,
UK; roswell.martin@gloucr-tr.
swest.nhs.uk

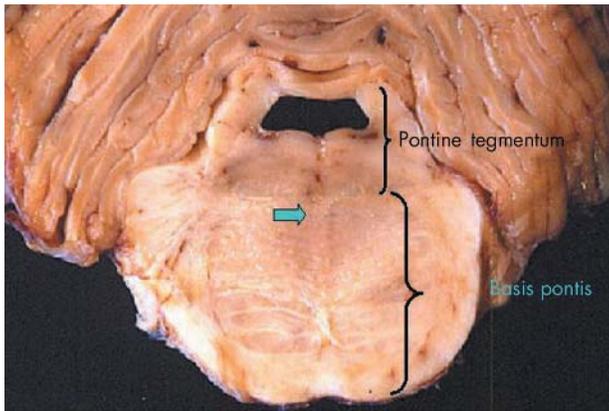


Figure 1 A reminder of the anatomy of the pons; although included to clarify the anatomical terms, a small lesion is in fact present, illustrating how easily such lesions may be missed on cursory pathological examination.

The movement disorders of EPM represent a treatable manifestation of the osmotic demyelination syndrome in that a rewarding symptomatic improvement can occur with dopaminergic treatment in those with parkinsonian features.

Other osmotic demyelination lesions

Other neurological lesions have been linked to CPM and EPM including cerebral cortical sclerosis and involvement of the posterior columns. Interestingly lesions in these regions were described in the original reports of CPM/EPM.

Clinical scenarios of CPM/EPM

Although initially described as occurring in alcoholics (three out of four of Adams’ original patients) and the undernourished, CPM/EPM has also been reported in adults with a variety of serious illnesses and after certain surgical procedures and even in toddlers with psychogenic polydipsia (table 2). It very rarely occurs in the absence of another significant illness. Hyponatraemia is the most common biochemical abnormality in medicine, yet despite this CPM/EPM is seen in a fairly restricted number of clinical situations, and is uncommon in some disorders where similar large osmolality shifts occur.

The association with alcoholism was the first to be noted and continues to be particularly frequent (in up to 40% of cases). The original authors pointed out pathological similarities to Marchiafava-Bignami disease (demyelination of the corpus callosum and other commissural fibre systems), a recognised complication of alcoholism. Wernicke’s is a not infrequent accompaniment (30% in pathological series). Some point out that alcohol itself interferes with sodium/water regulation by suppression of antidiuretic hormone (ADH), and inadequate nutrition of alcoholics is an obvious accompaniment.

CPM is a recognised complication of liver transplantation. In a 10 year retrospective series of 627 transplants it occurred in 2% of cases (but contributed only a tiny proportion to the overall neurological complication rate of 26%); it was conceded that this was likely to be an underestimate, the authors appreciating that postmortem studies showed a higher incidence. The possibility of EPM accounting for a proportion of the “acute encephalopathy”, the largest neurological complication following liver transplantation, does not appear to have been investigated.

Table 1 Lesions of central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) (in descending order of frequency)³

- ▶ Pons
 - ▶ Cerebellum
 - ▶ Lateral geniculate body
 - ▶ External capsule
 - ▶ Extreme capsule
 - ▶ Hippocampus
 - ▶ Putamen
 - ▶ Cerebral cortex/subcortex
 - ▶ Thalamus
 - ▶ Caudate nucleus
- The following 10% or less:*
- ▶ Claustrum
 - ▶ Internal capsule
 - ▶ Midbrain
 - ▶ Internal medullary lamella
 - ▶ Mamillary body
 - ▶ Medulla oblongata

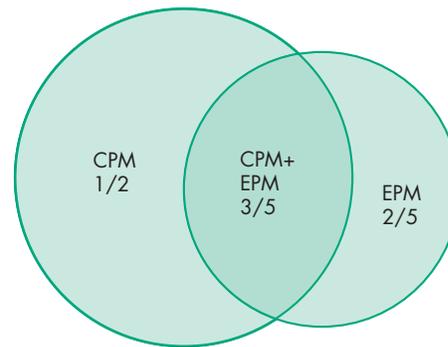


Figure 2 Relative proportions of central pontine myelinolysis (CPM), extrapontine myelinolysis (EPM), and CPM with EPM.

Osmotic demyelination, however, does not seem to occur with anything like the frequency one would expect in renal dialysis. It is thought that urea is acting in the renal failure patients as an “ineffective solute”—that is, it contributes to measured osmolality but as it easily crosses cell membranes does not contribute to tonicity, thus protecting from the rapid shifts in sodium which can occur in haemodialysis. Animal work suggests the mechanism may be more complex.

Table 2 Disease states associated with CPM/EPM, often more than one association present

- ▶ Alcoholism (common)
- ▶ Malnutrition (common)
- ▶ After prolonged diuretic use (frequent)
- ▶ Psychogenic polydipsia (rare if acute)
- ▶ Burns (infrequent, and often in context of hypernatraemia)
- ▶ Post-liver transplant (well recognised)
- ▶ Post-pituitary surgery (rare)
- ▶ Post-urolurgical surgery/gynaecological surgery, especially if involving glycine infusions (rare)

It is similarly very rare in diabetes, despite the pronounced shifts in osmolality that occur. Only a handful of cases exist in the literature (9 of 757 cases in a review of cases published before 2002).

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Pathology

The pons is divided anteroposteriorly into the basis pontis and the tegmentum. CPM, unless very severe, is predominantly a lesion of the basis pontis, sparing the tegmentum (figs 1 and 3). The original authors argued that the pathological process started in the central pons near the median raphe and that it spread out “like a brush fire” into the surrounding basis pontis. The lesion may extend up to the midbrain, but only very rarely down to the medulla. At its greatest extent it is confined in three dimensions to two pyramids side by side, their bases at the origin of the trigeminal nerve. Intriguing is the lesion shape and location. Its centre appears localised at a point equidistant from the CSF spaces around the brainstem. The localisation of the lesion within this region of the pons has long been one of the most puzzling aspects of the condition. One hypothesis rests on the fact that this is a region of maximal admixture of grey and white matter elements, which examination of any brain atlas stained for myelin will confirm. In support of this the lesions of EPM similarly seem to be in similar regions of grey–white apposition. The striking appearance of the lesion, which could not, it was argued, have been missed by earlier pathologists, lent support to the view that some new aetiological factor was at work from the 1950s onwards. Ultimately it was to be realised that this was a consequence of the “plastic revolution” and the widespread introduction of intravenous fluid therapy at that time.

Microscopically the lesion shows degeneration and loss of oligodendrocytes with preservation of axons unless the lesion is very advanced.

This author cannot see the value in changing the terminology of these conditions from the descriptive “central pontine myelinolysis” and “extra-pontine myelinolysis” to the vaguer “osmotic demyelination syndromes”. The original authors Adams, Victor, and Mancall¹ coined the term central pontine myelinolysis after careful thought. The location of

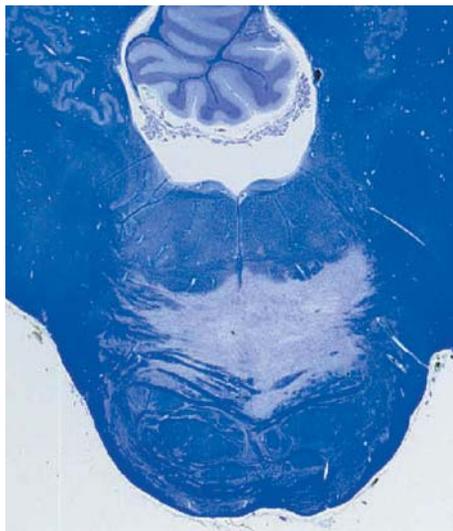


Figure 3 Pons with myelin stain (Luxol fast blue) showing lesion in basis pontis (CPM). Different case from gross specimen in fig 1.

the principal lesion is given, from which the neurological consequences of the lesion can be deduced. I suspect that more than once the visualisation of a lesion in the centre of the pons has triggered recognition of CPM by a clinical team. The term demyelination was deliberately avoided in order to distinguish this condition in which the myelin loss occurs without any obvious inflammatory infiltrate from the inflammatory nature of multiple sclerosis.

Aetiology of CPM/EPM

Adams and colleagues¹ argued that as the lesions were both *symmetrical* and *constant* in location, both of which are hallmarks of toxic or metabolic diseases, the aetiology was fundamentally biochemical. They were unable to appreciate the role of sodium (Na^+) because when these patients were collected (over 10 years in the 1950s) the measurement of serum electrolytes was not routine in clinical management. The only electrolyte disturbance they noted in their original paper was hypokalaemia, detected in one patient as a consequence of a change in the ECG.

Tomlinson in 1976 is generally credited with the suggestion that the *rapidity of correction* of Na^+ was the aetiological factor. This was followed up by the animal work of Laurenco (in dogs) and Kleinschmidt-DeMasters and Norenberg (in rats) who showed convincingly that the rate of correction was the key causative factor.⁴ The lesions in dogs are virtually identical to those of human cases and the clinical course and manifestations are identical. The animal work is so convincing that one can regard the aetiological factor to be beyond doubt. To understand how it happens we need to understand what happens in hyponatraemia.

Physiological changes in hyponatraemia and its correction

As water flows freely across the blood–brain barrier and cell membranes a fall in serum sodium (in the absence of a compensatory rise in other osmoles) will cause entry of water into brain cells and consequent brain swelling. Protective mechanisms come into play during the development of serum hypotonicity in all cell types to maintain cell volume, a process termed “regulatory volume decrease”. In the brain the first protective mechanism to act precedes this and is the forcing of interstitial sodium-rich fluid into cerebrospinal fluid (CSF) as a result of hydrostatic pressure.^{3,6} In the rat this occurs within minutes. Over the next few hours potassium is lost, and this is maximal after 24 hours. The maximum cation loss that occurs is 18% but this would put a theoretical limit on survivable hyponatraemia at 103 mmol/l if the loss of inorganic ions were the only available mechanism, and rats, like man can survive Na^+ concentrations below this.

It was realised that other solutes contribute and these are organic osmoles (such as myoinositol, taurine, and glutamate) which are lost over a day to a very few days, rendering the cell isotonic to the extracellular fluid and maintaining cell volume. Rat studies suggest that this process is complete in 48 hours (and hence the working definition of acute versus chronic hyponatraemia). The ion channels involved in the electrolyte shifts in the first phase of volume change are an area of active research.⁷ Those involved in steady state volume regulation—the “pump-leak balance mechanism”—are different from those involved in “regulatory volume decrease” in response to hypotonic challenge as well as from

Definitions

- ▶ Hyponatraemia: $\text{Na}^+ < 136 \text{ mmol/l}$
- ▶ Severe hyponatraemia: $\text{Na}^+ < 120 \text{ mmol/l}$
- ▶ Acute hyponatraemia: hyponatraemia known to be of less than 48 hours duration or developing at a rate of $> 0.5 \text{ mmol/hour}$
- ▶ Chronic hyponatraemia: hyponatraemia known to be of more than 48 hours duration or developing at a rate of $< 0.5 \text{ mmol/hour}$
- ▶ Tonicity (synonym: effective osmolality): that portion of total osmolality that has the potential to induce transmembrane water movement

the “regulatory volume increase” involved in hypertonic challenge.

The relative proportions of the contribution of organic and inorganic osmolytes involved in regulatory volume decrease in mice has been calculated. The most significant is potassium (29%), followed by chloride (19%); the amino acids (of which taurine, glutamine, glutamate, aspartate, and glycine are particularly significant) contribute 15%. Sodium is only the fourth most significant (13%). Other organic osmolytes contribute the rest.

Correction of hyponatraemia

The reaccumulation of electrolytes lost in response to a hypertonic environment is not the same process “in reverse” as their loss in adaptation to chronic hyponatraemia.

Once inorganic ion shifts have been exhausted, if the rate of rise of tonicity is faster than the rate at which organic osmoles can be synthesised and/or transported into the cell, the cell will shrink. It appears that oligodendrocytes are especially vulnerable to death, presumably from volume loss. It is perhaps here that the nutritional status of the patient plays its part, impairing the ability to regenerate organic osmoles. At present we cannot assess this ability, and so it is not really possible to determine a threshold rate of change that can be guaranteed to be universally safe. Recommendations for safe rates of Na^+ rise are based on animal models and published series of CPM.

It is with a sense of inevitability that one reads of a role for apoptosis being suggested in any disease. It is well established, however, that the persistent physical shrinkage of cells induced by hypertonic stress leads to cell death in a variety of cell types. Oligodendrocytes are particularly vulnerable to apoptosis in a number of disease states—a particularly striking example is hypoxic brain damage in infants. There is indeed some evidence for apoptosis in CPM. In a necropsy study of the ratio of pro- to anti-apoptotic markers, there appeared to have been a shift in favour of apoptosis in oligodendrocytes (the apoptotic related death markers—death receptor 3, Bax, and Bak—all showed modest increases).⁸ It is intriguing to note that apoptosis recruits a particular potassium channel (the two pore domain potassium channel) that is used for homeostatic volume regulation. Is it possible that osmotic stress via activation of these ion channels leads to inadvertent triggering of the apoptotic cascade?

Management of hyponatraemia

“Damned if we do, damned if we don’t” was one author’s view in an excellent review article on the management of

hyponatraemia, referring to the dilemma of rapid versus slow correction.⁵ Others have discussed the management of hyponatraemia in a critical review.⁹ They make the point that one cannot resolve this management dilemma by balancing the incidence of CPM in those treated rapidly with the mortality of hyponatraemic brain oedema treated “too slowly”, as one does not know that those patients in this latter group would have survived with rapid treatment; they may in fact have been beyond rescue. Only two out of 200 cases reviewed in the literature of CPM occurred as a consequence of rapid correction of acute hyponatraemia developing after admission to hospital, both in post-prostatectomy patients who had had bladder infusion of glycine and both hyperammonaemic.

It is a common experience of general physicians that the rapidity of rise in the concentration of Na^+ within the first day of treatment, even when avoiding hypertonic saline, and with every intention of supervising a gradual increase in Na^+ , may be surprisingly great: the Na^+ concentration seems to “run away”. This happens in animal models as well.

Mortality of severe hyponatraemia

In most series the mortality from severe hyponatraemia is between 40–50%. A few series, particularly in selected subgroups, such as those in the intensive therapy unit (ITU), have a lower but still significant mortality of about 10–20%.

This high mortality rate has led some authors to argue that the mortality is increased by slow correction and that the issue is one of “balancing” this mortality against the risk of inducing CPM/EPM. Their conclusions have met, however, with considerable controversy.^{4–6–9} The logic of this argument has been challenged as one cannot assume that rapid correction of severe symptomatic hyponatraemia in a patient will result in recovery—many of these patients are already brain dead from cerebral oedema at presentation, and beyond rescue however they are managed.

Evaluation of the cause of hyponatraemia

It is not uncommon for the cause of the hyponatraemia to remain somewhat clouded at the point when a neurological consultation is sought.

Pseudohyponatraemia

Pseudohyponatraemia is a problem that has not quite disappeared in the UK. If a significant non-aqueous phase is included in the volume of serum sampled the Na^+ result will be diluted accordingly. It is worth discussing this with your MLSO; in our hospital the blood gas analyser has a direct measuring Na^+ electrode, which can circumvent the problem. It is classically described in hyperlipidaemic states, hypertriglyceridaemia being the important factor, and in multiple myeloma (administration of intravenous immunoglobulin has the potential to mimic this)

Syndrome of inappropriate ADH (SIADH)

This may be over-diagnosed. In a retrospective series of patients admitted with severe hyponatraemia rarely had urine osmolality or urinary sodium checked, and “it is difficult to see how the cause of hyponatraemia could be clearly established”. Essential for diagnosis is euvoemia, normal renal function, and absence of hypothyroidism or Addison’s hypoadrenalism.

Cerebral salt wasting

This occurs most characteristically with subarachnoid haemorrhage. Its existence has always been somewhat controversial

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Treatment of acute hyponatraemia

The benign consequence of rapid correction of *acute* hyponatraemia is illustrated by a retrospective report of the lack of any sequelae of rapid correction of severe symptomatic acute hyponatraemia in 27 episodes among 13 patients with psychogenic polydipsia.¹⁰ Despite rapid and large rises in serum sodium, none of the patients had neurological sequelae. The difficulty in clinical practice is that it is extremely difficult to assess the chronicity of hyponatraemia in the patient admitted with severe hyponatraemia, so that if there is any doubt one should assume the hyponatraemia is chronic rather than acute.

Treatment of chronic hyponatraemia

Most authors seem to agree that the correction of *acute* hyponatraemia can be rapid; for *chronic* hyponatraemia the recommendations have shown an obvious trend (tables 3 and 4, fig 4). Discussion with colleagues suggests that the figure of not more than 10 mmol/l/day is the "consensus" figure most neurologists carry around in their head. The most recent recommendation is not in excess of 8 mmol/l/day. Some suggest stabilising the patient in a mild hyponatraemic state after the initial correction. Laurenco and Karp suggest that "it may be impossible to define a level of correction that is always completely free of risk". This problem is compounded as the treating physician has only indirect control over the rate of Na⁺ rise which may correct faster despite their best intentions.

There is no better example of the axiom that disorders of a metabolic nature should be treated at a rate commensurate with the rate at which they have developed. One should probably include any potassium (K⁺) correction in the total daily correction. Correction into hypernatraemic concentrations should definitely be avoided: why add insult to injury?

Other metabolic aetiologies

Hypernatraemia had already been reported in association with CPM before a landmark study of burns patients with CPM that firmly established hypernatraemia as an association.

Table 3 Published recommendations

- ▶ Too rapid is >20 mmol/l over 3 days (Norenberg)
- ▶ If Na⁺ <105 mmol/l correct at 2 mmol/l/hour for first 20 mmol/l, then allow to drift to normal. If Na⁺ ≥105 mmol/l correct at 2 mmol/l/hour to 125–130 mmol/l (Ayus 1985)
- ▶ Not >12 mmol/l/day for first day, and subsequent days slower (Stems 1987–1992)
- ▶ 2.5 mmol/l/hour and no more than 20 mmol/day (Berl 1990)
- ▶ Not >8 mmol/l/day (Oh 1995)
- ▶ 15 mmol/l in 24 hours (Kumar and Berl 1998)
- ▶ <10 mmol/l/day (Laurenco and Karp 1997), <10 mmol/l/day in first 24 hours and less on subsequent days (Karp and Laurenco 2000)
- ▶ Should not exceed 1–2 mmol/l/hour and never more than 8 mmol/l/day (Brown 2000)
- ▶ Should not exceed 8 mmol/l on any day of correction (Adrogué, 2000)

Although recommendations for slow correction have been standard for years, what is regarded as "slow" has changed.

Table 4 Practical management strategy

- ▶ What sodium shifts have occurred?
- ▶ Confirm that the cause of hyponatraemia has been reliably established
- ▶ Is there the opportunity to reinduce hyponatraemia?
- ▶ Has imaging been done? In a ventilated patient CT is acceptable; MRI desirable; repeat imaging necessary if negative
- ▶ Is the patient "locked-in"? Do nursing and medical staff appreciate this? Do relatives understand?
- ▶ Are relatives "in the picture" re prognosis?
- ▶ If EPM present is dopaminergic treatment an option?

CT, computed tomography; EPM, extra-pontine myelinolysis; MRI, magnetic resonance imaging.

Hypokalaemia has been reported as a possible trigger. However as a priori, even the lowest serum K⁺ compatible with life cannot produce a very significant shift in effective osmolality, it has not received the attention it might deserve. A review of published cases in 1994, in which the values of both Na⁺ and K⁺ were given, found that 66 of the 74 cases reported were hypokalaemic.¹¹

The significance of other electrolytes is less certain: associations with hypophosphataemia, magnesium, and lithium therapy have all been proposed, but in all cases either hyponatraemia was present or the Na⁺ was not measured at the beginning of the illness.

INVESTIGATIONS: EVOKED POTENTIALS AND IMAGING

Before computed tomography (CT) brainstem auditory evoked potentials were used, but modern imaging has superseded its use.

CPM can be seen on CT, but magnetic resonance imaging (MRI) is frequently striking (fig 5) and is the imaging technique of choice, having a greater sensitivity for CPM than CT and superior capacity for the demonstration of the lesions of EPM. Hyperintense lesions are seen on T2, and hypointense lesions on T1 weighted images. The lesions are non-contrast enhancing.

The timing of the appearance of lesions on MRI may be significantly delayed, and if the diagnosis remains likely a repeat imaging study at 10–14 days may reveal lesions not apparent on early scans. The reverse situation has been reported in which the MRI changes characteristic of CPM were seen without any pathological changes on postmortem examination one month after imaging (a 64 year old man with a heart transplant, Na⁺ 113 mmol/l to 134 mmol/l in 24 hours). The authors argued that what had been seen on MRI was reversible oedema.

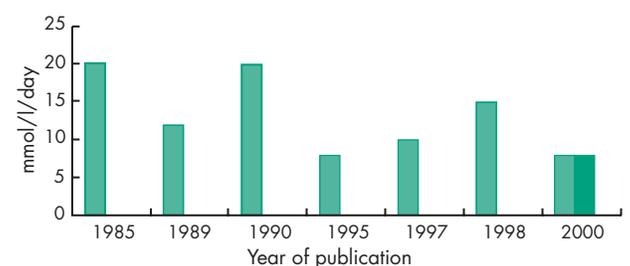


Figure 4 Maximum suggested correction of sodium in 24 hours.

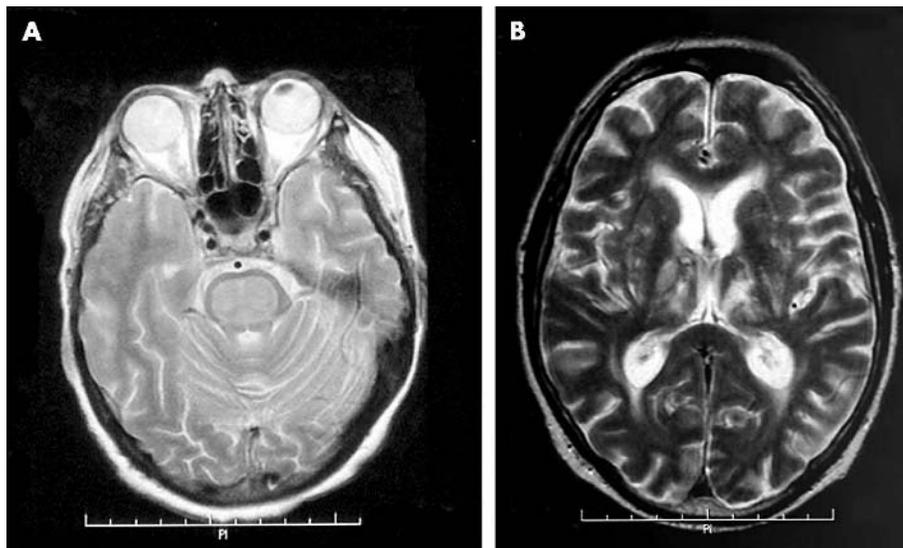


Figure 5 (A) Magnetic resonance image (MRI) of a 57 year old woman admitted with hepatic encephalopathy. History of alcohol consumption of half to a whole bottle of whisky a day. Admission Na^+ 113 mmol/l, K^+ 2.3 mmol/l, γGT 1067 mmol/l, bilirubin 106 mmol/l, alanine transaminase 133 mmol/l. Treated with intravenous normal saline; Na^+ 119 mmol/l at 36 hours and 128 mmol/l after a further 24 hours. Initial improvement, deterioration on 11th hospital day with pseudobulbar palsy and flaccid quadriplegia. (B) MRI of a 61 year old man with symmetrical lesions of EPM involving basal ganglia and thalamus; lesion of CPM was also present (MRIs courtesy of Dr Garrett McGann.)

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A recent series of cases found an absence of prognostic information from MRI, with neither the duration nor extent of abnormalities correlating with outcome.¹²

Diffusion weighted imaging (DWI) findings have been reported. DWI *might* have the capability of detecting lesions undetectable on T2. A single case report has just been published showing altered DWI in a patient within 24 hours of tetraplegia at a time when conventional MRI findings were inconspicuous.

Few of the cases currently being reported in the literature are supported by pathological evidence. The MRI appearance of CPM is so characteristic that one feels justified in making the diagnosis on MRI characteristics alone. This has the potential for misdiagnosis and may account for cases without characteristic shifts in Na^+ . It has been argued that large asymptomatic pontine lesions are unlikely to be CPM lesions.

TREATMENT OF CPM/EPM AND POTENTIAL FUTURE THERAPIES

There have been no trials. Case reports or very small series have tended to reinforce the perception that this condition has an excessively high mortality. At present supportive treatment is all that can be recommended with certainty.

Reports on small case series or single case reports of treatments including steroids, intravenous immunoglobulin, and thyrotrophin releasing hormone, have all shown good outcomes but are difficult to interpret for the above reason. Intriguing is the possible benefit of reinducing hyponatraemia, as has been reported in animal studies and two human cases.¹³ Animal work on the administration of organic osmolytes during the correction phase shows this to be a potential treatment.

PROGNOSIS

The prognosis of the osmotic demyelination syndrome has long been regarded as bleak, primarily because before CT/MRI this was a postmortem diagnosis: it was not until 10 years after its first description that the diagnosis was made in life, and that patient subsequently died of their disease. The introduction of CT and subsequently MRI allowed for confident diagnosis in life and inevitably survival and asymptomatic cases started to be reported. The most recent

Osmotic demyelination syndromes: key points

- ▶ Consider in a patient who has failed to recover as expected after a severe illness requiring intravenous fluids
- ▶ Consider in a patient manifesting “psychiatric” symptoms after such an illness, even if imaging is negative
- ▶ Na^+ rise *need not* be in excess of 10 mmol/l/day for condition to develop. There may be no “safe” limit for the rate of Na^+ rise; readers would be prudent to regular recommended limits of acceptable Na^+ rise at regular intervals as the recommended limit has steadily fallen
- ▶ Prognosis is not uniformly bad
- ▶ MRI changes may be delayed
- ▶ MRI severity is not prognostic
- ▶ Extra-pontine myelinolysis may manifest in a number of different ways, the clinical picture can evolve over days, and some of the manifestations may be symptomatically treatable
- ▶ The opportunity to present such cases at medical grand rounds should be considered in order to foster inter-speciality discussion of hyponatraemic management

large series of 34 cases showed that only two died, 10 survived but were left dependent, 11 had some deficits but were independent, and 11 recovered completely.¹² An individual prognosis is difficult. Neither clinical features nor extent of radiological change are predictive. In summary, the outcome may be death, disability, or recovery to a virtually normal level of function.

One major practical problem is that from the relatives’ point of view there has been a deterioration in the patient’s condition since admission which has usually followed a period of initially gratifying improvement. This situation would be easier for everyone to deal with if the possibility of late deterioration is discussed as soon as severe hyponatraemia is detected and correction is begun.

It is important to clarify with all medical staff that good recovery *is* possible so as not to misinform resuscitation decisions.

CONCLUSION

The osmotic demyelination syndrome is a complication of treatment of patients with profound, life threatening

hyponatraemia. It occurs as a consequence of a rapid rise in serum tonicity in individuals with chronic severe hyponatraemia who have made intracellular adaptations to the prevailing hypotonicity. Elevation in serum sodium is the overwhelming contributor to the rise in tonicity, but potassium elevation may contribute. Malnutrition and alcoholism seem to predispose. Evidence for other electrolyte shifts (with the exception of prolonged hypernatraemia) as causative is flimsy.

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