ORIGINAL PAPER

# Central pontine myelinolysis: historical and mechanistic considerations

**Michael D. Norenberg**

**Abstract** Central pontine myelinolysis (CPM) is a demyelinating condition affecting not only the pontine base, but also involving other brain areas. It usually occurs on a background of chronic systemic illness, and is commonly observed in individuals with alcoholism, malnutrition and liver disease. Studies carried out 25–30 years ago established that the principal etiological factor was the rapid correction of hyponatremia resulting in osmotic stress. This article reviews progress achieved since that time on its pathogenesis, focusing on the role of organic osmolytes, the blood–brain, barrier, endothelial cells, myelinotoxic factors triggered by osmotic stress, and the role of various factors that predispose to the development of CPM. These advances show great promise in providing novel therapeutic options for the management of patients afflicted with CPM.

**Keywords** Apoptosis · Blood–brain barrier · Central pontine myelinolysis · Demyelination · Endothelial cells · Hepatic encephalopathy · Hyponatremia · Organic osmolytes · Osmotic stress

M. D. Norenberg (✉)
Departments of Pathology,
University of Miami School of Medicine,
PO Box 016960, Miami, FL 33101, USA
e-mail: mnorenbe@med.miami.edu

M. D. Norenberg
Veterans Affairs Medical Center,
Miami, FL, USA

M. D. Norenberg
Departments of Biochemistry & Molecular Biology,
University of Miami Miller School of Medicine,
Miami, FL, USA

## Introduction

Adams and colleagues (1959) described a demylinating disorder that symmetrically affected the central portion of the pontine base (Fig. 1). It predominantly occurred in alcoholic, malnourished and chronically ill individuals who presented with dysarthria, dysphagia, quadriplegia and mutism. Pathologically, it was characterized by loss of oligodendrocytes and myelin, and by the preservation of neurons and axons, along with macrophage infiltration and astrocytic activation. In contrast to multiple sclerosis, the prototype demyelinating disease, an inflammatory component was absent. This feature prompted the authors to apply the term myelinolysis rather than demyelination; hence the designation of central pontine myelinolysis (CPM).

As additional cases were identified, it became apparent that lesions were not confined to the pons, but also occurred in the basal ganglia, thalamus, gray–white junction of cerebral and cerebellar cortices, lateral geniculate and at other sites, so-called extrapontine CPM (Klavins 1963; Wright et al. 1979; Goldman and Horoupian 1981). It also became clear that while a background of alcoholism was common, in many cases a history of alcoholism was absent, and that such condition even occurred in children (Kepes et al. 1965; Rosman et al. 1966). Additionally, it became evident that almost all patients had chronic medical conditions, including cancer, liver disease, liver transplantation, sepsis, burns and fluid and electrolyte disorders. In other words, CPM never occurred in isolation, but rather it was seen as a complication of a pre-existing medical condition.

In their initial report, Adams and colleagues (1959) commented that CPM appeared to be "a new disease". The authors reviewed the literature for the previous 75 years and were unable to find any cases resembling CPM, clinically

**Fig. 1** Classic histopathology of the pons in CPM showing a symmetrical, central bat-wing area of demyelination affecting most of the pontine base. Luxol-fast blue/PAS

or pathologically. Aleu and Terry (1963) noted that while alcohol had been around a long time, CPM was new, suggesting the possibility that some iatrogenic agent(s) used in maintaining patients perhaps might be involved. The potential iatrogenicity became an even stronger possibility as CPM always occurred in a hospital setting; i.e., no patient had ever been admitted to a hospital with symptoms of CPM, and proved to have such pathology at postmortem examination. Messert and co-workers (1979) made the important observation that the recognition of CPM corresponded with the advent of intravenous fluid therapy in the late 1950's ("plastic revolution"). For general reviews on CPM, see (Goebel and Zur 1976; Brown 2000; Lampl and Yazdi 2002; Martin 2004; Kleinschmidt-DeMasters et al. 2006).

**Fluid and electrolyte derangements**

Among the various factors associated with CPM, fluid and electrolyte derangements took on a dominant position. The first such report was given by Hugh H. Adams (1962). This was followed by 20 articles describing this finding (reviewed in Burcar et al. 1977). In 1976 we encountered a striking case of CPM in a 50-year-old woman with a past history of alcoholism, hypertension and on diuretics. Six days before admission she became ill with nausea, vomiting, diarrhea, malaise and generalized weakness. Two generalized seizures prompted her admission. The neurological examination was normal except for absent deep tendon reflexes. Initial laboratory data disclosed a serum sodium of 96 mEq/l. The hyponatremia was corrected within 24 h with water restriction and hypertonic saline. The patient gradually improved but on the fourth hospital day she became stuporous, unresponsive to verbal commands, and subsequently developed quadriparesis. Her condition remained unchanged and she died two months

later from pulmonary and urinary tract infections. At autopsy, CPM was identified.

We then reviewed our own cases of CPM and those described in the English literature (Burcar et al. 1977). We identified 15 cases in our files, all of whom had hyponatremia (96–130). Review of the literature disclosed 80 cases of CPM, in which electrolyte values were reported in only 30 cases; of these, 12 had hyponatremia. Adding our cases to the 12 reported in literature, we identified hyponatremia in 61% of cases with CPM. We then reviewed the histories of patients with CPM in whom electrolyte data was not documented, specifically looking for the possibility that some of these patients might have had a condition likely to be associated with hyponatremia (compulsive water drinking, hemodialysis, inappropriate secretion of antidiuretic hormone, severe renal disease, history of diarrhea or vomiting, thyroid or adrenal failure). The review showed that 69 of the 80 patients (86%) either had documented hyponatremia, or had a plausible cause of hyponatremia. At about the same time, Tomlinson and colleagues (1976) reported two additional patients with a history of protracted vomiting and drowsiness who developed severe hyponatraemia (serum sodium 96–100 mEq/l). They noted that correction of electrolyte abnormalities was accompanied by a deterioration in the level of consciousness, quadriparesis, dysphasia and mutism. Postmortem examination showed that the patients had CPM.

The findings of our study propelled us to examine whether we could identify CPM-like lesions in rats made hyponatremic. Dr. Roger Riepe, a Neuropathology Fellow at the University of Colorado, took on this task. Despite using many protocols (varying the severity of hyponatremia, speed of sodium changes and duration of hyponatremia) he did not identify any neuropathological changes, other than minor Alzheimer type II-like astrocyte changes, similar to those seen in patients with hepatic encephalopathy.

**Evolution of a hypothesis**

While it became clear that hyponatremia alone was not responsible for CPM, the association of hyponatremia with CPM was simply too difficult to discard. A number of isolated events subsequently evolved to disclose the likely relationship between hyponatremia and CPM. In 1979 Dr. Kevin Leslie, a Pathology resident at the University of Colorado, performed an autopsy on a patient who ultimately was shown to have CPM. The patient was jaundiced and the lesion in the pons had a striking green discoloration (Fig. 2). Such discoloration is usually seen when a breakdown of the blood–brain barrier (BBB) has occurred, allowing albumin-bound bile pigment to exit the blood
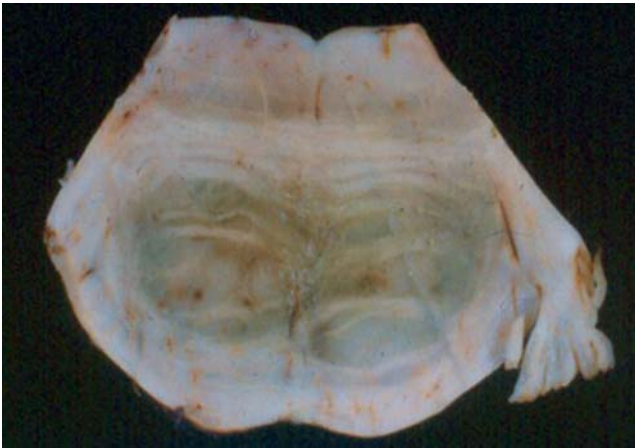
**Fig. 2** Gross appearance of the pons in a case of CPM. The patient was jaundiced and the lesion displayed a green discoloration. Such changes are indicative of a breakdown of the blood–brain barrier

stream. This egress of bile pigment can only occur in the presence of an increase in capillary permeability. Review of the literature noted several reports describing a similar green discoloration of the pons in patients with CPM who had concurrent liver disease and jaundice (Chason et al. 1964; Shurtliff et al. 1966; Monteiro 1971). James Powers and Paul McKeever (1976) had also described potential defects in the BBB in CPM.

This author was also aware of articles by Feigin and Budzilovich (1978) and Feigin et al. (1973) showing that chronic edema led to demyelination. The authors speculated that a blood-derived myelinolytic factor was responsible for the demyelination. This author was likewise familiar with work showing that the BBB could be opened by the intravenous administration of hypertonic saline (Brightman et al. 1973; Rapoport 1976). Such an effect was deemed to be a consequence of endothelial cell dehydration and shrinkage leading to an impairment of endothelial tight junctions. In fact, neurosurgeons were beginning to use this strategy to deliver chemotherapeutic agents that were otherwise impermeable to the BBB (Neuwelt et al. 1982).

Thus, there was a loose assortment of facts—first, CPM was somehow associated with hyponatremia, the BBB was compromised and the lesions occurred principally in the pons but also at other sites. It was also known that chronic edema, presumably due to a disturbance in the BBB, was associated with demyelinating lesions and that hyperosmotic stress was able to open the BBB. But these were simply facts without any integrating or coherent aspect relevant to the pathogenesis of CPM. This dramatically changed one morning in 1979 while preparing to review the histology of a case of CPM. The prosector was Scott VendenBerg, a first year Pathology resident at the University of Colorado. We reviewed what was then known about CPM, and I mentioned our recent studies on the potential

role of hyponatremia. In a nonchalant manner Scott said "I wonder whether CPM is due to osmotic stress?". I was not exactly sure what Scott had in mind when he uttered that phrase—but that was a quintessential moment as this comment immediately crystalized all of the disjointed facts into a logical mechanism, potentially explaining the pathogenesis of CPM. What became seemingly obvious was that hyponatremia per se was not the inciting factor in CPM; rather, its correction was the culprit as this would result in hyperosmotic stress, endothelial dehydration and opening of the BBB, thereby allowing the as yet mysterious myelinolytic factors to enter the brain.

This mechanism also explained why the pons and other brain areas affected in CPM were involved. It had earlier been underscored by Okeda (1974), and by Messert and colleagues (1979) that a unique aspect of the topography of those sites was their grid-like or checker-board architecture as these regions were composed of a great admixture of gray and white matter (Fig. 3). The importance of this architecture is based on the fact that gray matter contains 10-times more capillaries than white matter. As such, if a myelinotoxic factor from blood was indeed responsible for the demyelination, that factor would be enriched in gray matter, while the substrate of that factor, myelin, would be present in the immediately adjacent white matter. If the hypothesis was correct, areas with a rich gray–white matter admixture would therefore be at greatest risk for demyelination. Of all areas of the human brain, the pons displays the greatest degree of gray–white matter admixture.

## Testing a hypothesis

To examine the validity of this mechanism, Kevin Leslie and Andrew Robertson, a Neurology resident rotating in Neuropathology, were given the task of reviewing all of our
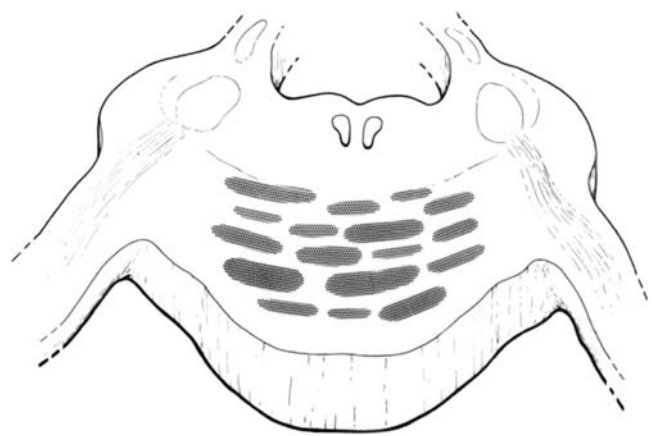


**Fig. 3** Sketch of the human pons showing a close admixture of white matter bundles (*gray zones*) within the white background (*gray matter*)

cases, in addition to those reported in the literature, to examine whether or not a period of rapid correction of hyponatremia had occurred prior to the onset of CPM. Simultaneously, Bette Kleinschmidt- DeMasters, who had just joined the laboratory as a Neuropathology fellow, examined the same issue experimentally in the rat.

The clinical study study showed that all of our 15 cases of CPM were hyponatremic (some mildly so), and had experienced a 20–30 mEq/l rise in serum sodium 3–10 days (mean, 6 days) before neurological symptoms developed. A comparable group of patients showing a similar degree of hyponatremia, but who did not develop CPM, had considerably lesser or slower rises in sodium levels following treatment of hyponatremia (Leslie et al. 1980; Norenberg et al. 1982). Similar findings were observed in rats made hyponatremic with vasopressin and water injection and then treated with hypertonic saline (Kleinschmidt-DeMasters and Norenberg 1981). Demyelinative lesions were observed in the midbrain, thalamus and striatum, sites with extensive gray–white matter admixture. In the rat, the pons consists of mostly white matter, and lesions were not observed at this site. Hyponatremia alone or slow correction of hyponatremia failed to produce lesions. At about the same time, Robert Laureno at Case-Western University using a similar protocol, found comparable findings in dogs, but additionally noted the presence of pontine lesions (the architecture of the pons in humans and dogs are similar) (Laureno 1980, 1983). Subsequent studies by other groups found similar pathological changes in rats (Ayus et al. 1985; Rojiani et al. 1987; Verbalis and Martinez 1991) and rabbits (Illowsky and Laureno 1987).

While clinical and experimental data pointed to a rapid correction of hyponatremia in patients with CPM, this did not always occur. Subsequent to our original report (Norenberg et al. 1982), we identified a normonatremic (139 mEq/l) patient with hepatic encephalopathy who was treated with lactulose (an agent known to cause hypernatremia). On the 10th hospital day he became restless and confused, at which time the sodium had risen to 171 mEq/l. He died on the 20th hospital day from sepsis. A small, recent, demyelinating lesion was found in the center of the pontine base (Norenberg 1983). Similar findings were reported by other investigators (McKee et al. 1988; Riggs and Schochet 1989). Thus, hyponatremia may rarely not occur in the course of CPM, but a rise in serum osmolarity due to sodium (or perhaps another osmolyte, e.g., glucose) is always present.

Another aspect that became apparent in the analysis of rapid correction of hyponatremia in CPM was the duration of hyponatremia prior to its correction (Norenberg 1984). This study disclosed that those patients who experienced hyponatremia for a short period of time (hours to a few days) did not develop CPM (Norenberg 1984). By contrast, those who were hyponatremic for 1 week or longer, all developed CPM. This aspect was tested experimentally in rats: one group was kept hyponatremic for 3 days while another group was hyponatremic for 1 day. Both groups were then treated with hypertonic saline (Norenberg and Papendick 1984). The 3-day treated hyponatremic rats developed more numerous and more severe lesions, as compared to the 1-day treated rats. This data strongly suggested that chronicity of hyponatremia was a crucial factor in the pathogenesis of CPM.

## Contemporary mechanistic concepts

The precise sequence of events by which hyponatremia, or more importantly the hypernatremia/hyperosmolarity following its rapid correction, leads to demyelination is still unclear, but significant progress has evolved over the last 25 years.

Cell volume regulation and organic osmolytes

Following acute hyponatremia, brain cells swell and as an adaptation, they release electrolytes, principally $Na^+$, $K^+$, $Cl^-$. Following rapid correction of hyponatremia, usually with hypertonic saline, $Na^+$ and $Cl^-$ reaccumulate rapidly and osmotic equilibrium is restored (for reviews, see (Strange 1992, 1993). A different set of events occurs, however, if the patient has been chronically hyponatremic (1 week or longer). Not only are $Na^+$, $K^+$, $Cl^-$ lost, but additionally the cells lose organic osmolytes (principally myo-inositol, taurine, glutamine, glutamate, creatine, phosphocreatine, glycerophosphorylcholine), formerly known as "idiogenic osmoles". The cells thereby achieve osmotic equilibrium, but at a lower osmotic set-point.

Following the rapid correction of chronic hyponatremia with hypertonic saline cells become dehydrated. Ions reaccumulate quickly (within minutes) followed by osmotically obligated water, whereas organic osmolytes take about 5 days or more to do so. The initial high concentration of ions is stressful to the cells ("perturbing solutes") as it interferes with the maintenance of proper protein structure and function. By contrast, organic osmolytes tend to maintain normal protein structure and function ("compatible solutes"). These effects are a consequence of ions directly binding to proteins causing them to denature/misfold, in contrast to organic osmolytes that do not bind to proteins and maintain proteins in their native, unfolded configuration. For review on cell volume regulation, and especially the protective role of organic osmolytes, see reviews by Burg et al. (2007) and Burg and Ferraris (2008).

While the potential involvement of organic osmolytes in experimental CPM was earlier noted in passing (Norenberg

1983; Norenberg and Papendick 1984), it was not until 1987 that Thurston and colleagues (1987) first reported that rapid correction of hyponatremia was associated with a reduction of amino acids (especially taurine), creatine and citric acid cycle intermediates, thereby highlighting the potential importance of organic osmolytes in the production of brain lesions following rapid correction of chronic hyponatremia. A more comprehensive analysis of such loses of organic osmolytes following hyponatremia was provided by Verbalis and Gullans (1991).

A detailed examination of the role of organic osmolytes following hyponatremia and its correction was performed by Lien et al. (1991). These workers reported that following hyponatremia, *myo*-inositol, glycerophosphorylcholine, phosphocreatine/creatine, glutamate, glutamine, and taurine levels were depressed. With rapid correction, reaccumulation of these organic osmolytes, except glycerophosphorylcholine, was delayed. The authors concluded that rapid correction of hyponatremia was associated with an overshoot of brain sodium and chloride levels along with a low organic osmolyte level, and that the high cerebral ion concentrations in the absence of adequate concentrations of organic osmolytes may have contributed to the development of CPM. Similar findings were documented by Verbalis and Gullans (1993) in their experimental work in rats with CPM. Interestingly, Lien (1995) found a good correlation between the delayed accumulation of organic osmolytes following correction of hyponatremia and the localization of demyelinating lesions. While the basis for these findings were not discussed, a review of the data clearly indicates that the areas most affected correspond to those possessing the greatest extent of gray–white matter admixture.

Subsequently, it was shown that renal failure and exogenous urea (an organic osmolyte) prevented myelinolysis following rapid correction of experimental hyponatremia (Soupart et al. 2000). Soupart and co-workers (2002) then showed that such protection by azotemia was due to the rapid reaccumulation of brain organic osmolytes after correction of hyponatremia. How urea stimulates the uptake of other organic osmolytes is not known.

All of the above studies support a major role of organic osmolytes deficiency during the correction phase of hyponatremia. The importance of this concept is accentuated by the report of Silver et al. (2006) showing that treatment of rats during the correction phase with *myo*-inositol (along with saline) improved the survival of rats and diminished the number of demyelinating lesions. These important findings have great therapeutic relevance for patients with CPM.

Endothelial cells and the blood–brain barrier

As was noted above, a breakdown of the BBB is a feature of CPM in humans, and speculations were offered as to how such a defect in the BBB might contribute to the development of CNS lesions. The breakdown in the BBB was subsequently reported in experimental CPM (Rojiani et al. 1994a; Sugimura et al. 2005; Murase et al. 2006), and glucocorticoids, agents well known to reinforce the BBB (Hedley-Whyte and Hsu 1986; Hoheisel et al. 1998; Sinton et al. 2000; Rosenberg et al. 1996), were shown to reduce the number of lesions in experimental animals (Rojiani et al. 1987; Oh et al. 1990; Sugimura et al. 2005; Ke et al. 2006; Murase et al. 2006) and in humans (Schneck et al. 1978; Sterns et al. 2007).

The means by which osmotic stress brings about an opening of the BBB is not clear. It is likely that dehydration and shrinkage of endothelial cells creates a mechanical injury to endothelial tight junctions. It is also possible such osmotic injury may elicit the release of agents harmful to the integrity of endothelial tight junctions. It has been reported that nitric oxide may contribute to a breakdown of the BBB (Liu et al. 2001), and Ke and co-workers (2006) provided evidence that inducible nitric oxide synthase was overexpressed in experimental CPM and that such overexpression was inhibited by dexamethasone.

How a disturbance in the BBB leads to demyelination is also not clear. As noted above, there were suggestions that blood-derived factors may contribute to demyelination. More recently it was shown that complement is toxic to oligodendrocytes in culture (Wren and Noble 1989; Scolding et al. 1989; Wing et al. 1992) and to myelin (Cyong et al. 1982; Vanguri et al. 1982). Adler et al. (1995) suggested such a mechanism in CPM. The same research group subsequently showed marked increases in IgG and C3d complement immunostaining in experimental CPM (Baker et al. 2000). The staining intensity also correlated with the degree of neurological impairment.

It is also possible that direct osmotic injury to endothelial cells may result in the release of agents that have damaging effects on myelin and/or oligodendrocytes. Endothelial cells are known to contain and release high amounts of the neutral protease, plasminogen activator (Todd 1972). By the formation of plasmin, plasminogen activator may lead to demyelination as plasmin has been shown to hydrolyze myelin basic protein (Cammer et al. 1978). In preliminary studies we found a marked increase in plasminogen activator activity following the rapid correction of hyponatremia (Norenberg and Bell 1982). Such activation was inhibited by dexamethasone, which also blocked the development of demyelinating lesions. Other factors known to be released by endothelial cells that are capable of injuring both the BBB and oligodendroglial cells, such as cytokines (Vadeboncoeur et al. 2003; Verma et al. 2006; Simka 2009) may also be involved.

In this regard, recent preliminary studies by Joshua Johnstone, a Neuroscience graduate student and Dr.

Arumugam Jayakumar, both at the University of Miami, have shown that osmotically stressed endothelial cells in culture release a factor(s) that is lytic to cultured oligodendrocytes. The nature of this factor is yet to be determined. However, these findings indicate that osmotically injured endothelial cells, independent of any breakdown of the BBB, are capable of damaging oligodendrocytes.

Apoptosis

While comments regarding a role of apoptosis in CPM were proposed by Ashrafian and Davey (2001), the first documented report was given by DeLuca and colleagues (2002). To some extent this was not surprising as oligodendrocytes are well known to undergo apoptosis following different forms of injury (Ludwin 1997), and may even be the neural cell that most frequently undergoes this form of cell death. In their elegant electron microscopic study, Rojiani and colleagues (1994b) illustrated oligodendroglial changes that undoubtedly represent early apoptosis. The term apoptosis was not used in that publication as it was not yet part of the lexicon. We had also found similar electron microscopic changes (Fig. 4) (Norenberg 1981). Even by light microscopy (in retrospect), oligodendroglia show unmistakable changes indicative of apoptosis (Norenberg and Papendick 1984).

Other implicated factors

While osmotic stress secondary to rapid correction of hyponatremia represents a critical factor in the pathogenesis of CPM, a number of published reports have not described such an outcome. Careful review of these reports, however, did not provide sufficient electrolyte data for analysis; it was unclear whether the sodium data noted corresponded with the onset of CPM (i.e., was the right epoch examined); lack of pathological data that indeed CPM was the offending lesion; and the chronicity of hyponatremia was not taken into account. Similar concerns have been expressed by other investigators (Karp and Laureno 2000). These caveats aside, in the author's experience, as well as based on the literature, there have been cases where similar changes in the magnitude of electrolyte fluxes have resulted in markedly different degrees of severity of CPM lesions. This questions whether other events or factors might predispose to, or possibly prevent the development of CPM.

Foremost among these events is preexisting liver disease (Shurtliff et al. 1966; Goebel and Zur 1972), especially orthotopic liver transplantation (Starzl et al. 1978; Estol et al. 1989; Wszolek et al. 1989; Boon et al. 1991; Ferreiro et al. 1992; Ghidoni et al. 1994; Bonham et al. 1998) which in some series the incidence of CPM was as high as 30% (Singh et al. 1994). The explanation for this propensity is not fully understood. However, patients with liver disease often have hyponatremia (Reynolds 1980). A more likely possibility is that these patients are malnourished and it is possible that their intracellular *myo*-inositol levels are diminished. Using NMR spectroscopy, brain *myo*-inositol levels have indeed been found reduced in patients with liver disease (Kreis et al. 1992; Gupta et al. 1993; Pujol et al. 1996; Häussinger et al. 1994), and in rats with portacaval anastomosis (a model of chronic hepatic encephalopathy) (Córdoba et al. 1996). Cultured astrocytes treated with ammonia (the principal toxin in hepatic encephalopathy) show reduced *myo*-inositol levels. *myo*-Inositol is actively taken up by astrocytes (Isaacks et al. 1994, 1999b; Lubrich et al. 2000), and ammonia impairs this uptake (Isaacks et al.



**Fig. 4 a** Early ultrastructural change in oligodendrocytes in experimental CPM in rats showing nuclear irregularity and chromatin clumping. **b** Later stage of CPM showing nuclear fragmentation characteristic of apoptosis. ×4,600
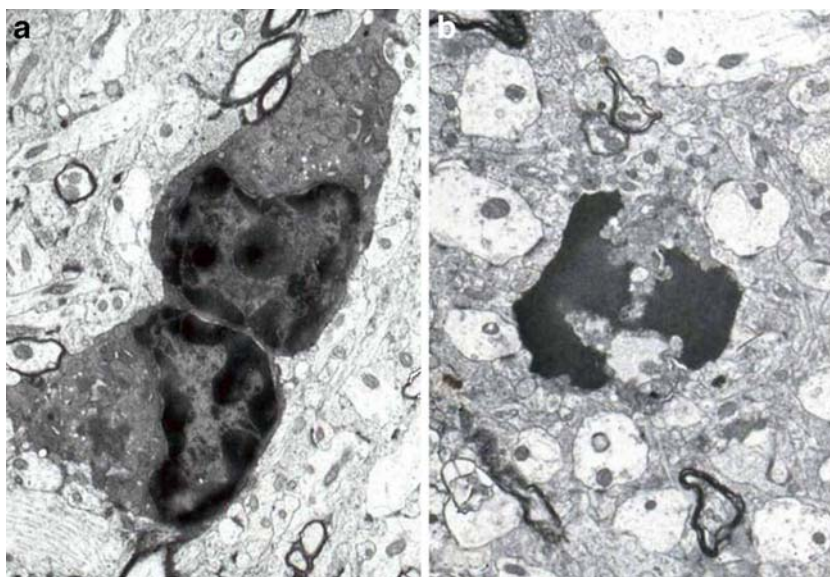
1999a). It is of interest that other organic osmolytes such as taurine and glycerophosphorylcholine are also reduced in humans with hepatic encephalopathy (Bluml et al. 1998), and in rats with a portacaval anastomosis (Córdoba et al. 1996). As noted above, such deficiencies in organic osmolytes may greatly sensitize the brain to hyperosmotic stress. In view of the potential role of apotosis in the mechanism of oligodendroglial cell death, it is worth commenting that in addition to its protection against hyperosmotic stress, *myo*-inositol also has antiapoptotic properties (Alfieri et al. 2002).

Other factors that have been implicated in the mechanism of CPM include hypophosphatemia (Qadir et al. 2005; Michell et al. 2003; De Broucker et al. 1989) and hypokalemia (Lohr 1994; Heng et al. 2007). It is noteworthy that phosphate is required for the synthesis of two organic osmolytes, phosphocreatine, and glycerophosphorylcholine. As with *myo*-insitol, such deficiency may predispose to hyperosmotic stress. The means by which hypokalemia seinsitizes the CNS to CPM (if it does) is not apparent.

## Summary and perspectives

CPM is a demyelinating condition affecting principally the pons and in most instances caused by a rapid correction of chronic hyponatremia (of at least several days duration). The hyperosmotic stress created by the rapid correction causes endothelial injury and opening of the blood–brain barrier resulting in the release of myelinotoxic or oligodendroglial destructive factors. The condition in many instances is preventable, but not always. Significant knowledge has accrued over the past two decades regarding its mechanisms leading to novel therapeutic possibilities for the treatment of patients prone to develop CPM.

On a personal note, the exploration of mechanisms involved in CPM was, and has been, an exciting journey that has also yielded important insights into the mechanisms of other neurological disorders. While I have not been actively involved in CPM research in more than two decades, I marvel at the achievements of many investigators, and look forward to future advances in our understanding of this fascinating neurological disorder.

## References

Adams JH (1962) Central pontine myelinolysis. In: Jacob H (ed) IV International Congress of Neuropathology, vol 3. Georg Thieme Verlag, Stuttgart, pp 303–308

Adams RD, Victor M, Mancall EL (1959) Central pontine myelinolysis: a hitherto undescribed disease occurring in alcoholic and malnourished patients. AMA Arch Neurol Psychiat 81:154–172

Adler S, Verbalis JG, Williams D (1995) Effect of rapid correction of hyponatremia on the blood–brain barrier of rats. Brain Res 679:135–143

Aleu FP, Terry RD (1963) Central pontine myelinolysis. Arch Path 76:140–146

Alfieri RR, Cavazzoni A, Petronini PG, Bonelli MA, Caccamo AE, Borghetti AF, Wheeler KP (2002) Compatible osmolytes modulate the response of porcine endothelial cells to hypertonicity and protect them from apoptosis. J Physiol 540:499–508

Ashrafian H, Davey P (2001) A review of the causes of central pontine myelinosis: yet another apoptotic illness? Eur J Neurol 8:103–109

Ayus JC, Krothapalli RK, Armstrong DL (1985) Rapid correction of severe hyponatremia in the rat: histopathological changes in the brain. Am J Physiol Renal Fluid Electrolyte Physiol 248:F711–F719

Baker EA, Tian Y, Adler S, Verbalis JG (2000) Blood–brain barrier disruption and complement activation in the brain following rapid correction of chronic hyponatremia. Exp Neurol 165:221–230

Bluml S, Zuckerman E, Tan J, Ross BD (1998) Proton-decoupled 31P magnetic resonance spectroscopy reveals osmotic and metabolic disturbances in human hepatic encephalopathy. J Neurochem 71:1564–1576

Bonham CA, Dominguez EA, Fukui MB, Paterson DL, Pankey GA, Wagener MM, Fung JJ, Singh N (1998) Central nervous system lesions in liver transplant recipients: prospective assessment of indications for biopsy and implications for management. Transplantation 66:1596–1604

Boon AP, Carey MP, Adams DH, Buckels J, McMaster P (1991) Central pontine myelinolysis in liver transplantation. J Clin Pathol 44:909–914

Brightman MW, Hori M, Rapoport SI, Reese TS, Westergaard E (1973) Osmotic opening of tight junctions in cerebral endothelium. J Comp Neurol 152:317–325

Brown WD (2000) Osmotic demyelination disorders: central pontine and extrapontine myelinolysis. Curr Opin Neurol 13:691–697

Burcar PJ, Norenberg MD, Yarnell PR (1977) Hyponatremia and central pontine myelinolysis. Neurology 27:223–226

Burg MB, Ferraris JD (2008) Intracellular organic osmolytes: function and regulation. J Biol Chem 283:7309–7313

Burg MB, Ferraris JD, Dmitrieva NI (2007) Cellular response to hyperosmotic stresses. Physiol Rev 87:1441–1474

Cammer W, Bloom BR, Norton WT, Gordon S (1978) Degradation of basic protein in myelin by neutral proteases secreted by stimulated macrophages: a possible mechanism of inflammatory demyelination. Proc Natl Acad Sci USA 75:1554–1558

Chason JL, Landers JW, Gonzalez JE (1964) Central pontine myelinolysis. J Neurol Neurosurg Psychiat 27:317–325

Córdoba J, Gottstein J, Blei AT (1996) Glutamine, myo-inositol, and organic brain osmolytes after portacaval anastomosis in the rat:

implications for ammonia-induced brain edema. Hepatology 24:919–923

Cyong JC, Witkin SS, Rieger B, Barbarese E, Good RA, Day NK (1982) Antibody-independent complement activation by myelin via the classical complement pathway. J Exp Med 155:587–598

De Broucker T, Rueff B, Hammel P, Hadengue A (1989) Hypophosphoremia: a possible cause of central pontine myelinolysis. Presse Med 18:1166

DeLuca GC, Nagy Z, Esiri MM, Davey P (2002) Evidence for a role for apoptosis in central pontine myelinolysis. Acta Neuropathol 103:590–598

Estol CJ, Faris AA, Martinez AJ, Ahdab-Barmada M (1989) Central pontine myelinosis after liver transplantation. Neurology 39:493–498

Feigin I, Budzilovich GN (1978) The role of edema in diffuse sclerosis and other leukoencephalopathies. J Neuropathol Exp Neurol 37:326–357

Feigin I, Budzilovich G, Weinberg S, Ogata U (1973) Degeneration of white matter in hypoxia, acidosis and edema. J Neuropathol Exp Neurol 32:125–143

Ferreiro JA, Robert MA, Townsend J, Vinters HV (1992) Neuropathologic findings after liver transplantation. Acta Neuropathol 84:1–14

Ghidoni P, Di Bella C, Masini T, Paone G, Matturri L (1994) Central pontine and extrapontine myelinolysis after orthotopic liver transplantation. Transplant Proc 26:3602–3603

Goebel HH, Zur PH (1972) Central pontine myelinolysis. A clinical and pathological study of 10 cases. Brain 95:495–504

Goebel HH, Zur PH (1976) Central pontine myelinolysis. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology, vol 28. North Holland Publishing Co, Amsterdam, pp 285–316

Goldman JE, Horoupian DS (1981) Demyelination of the lateral geniculate nucleus in central pontine myelinolysis. Ann Neurol 9:185–189

Gupta RK, Saraswat VA, Poptani H, Dhiman RK, Kohli A, Gujral RB, Naik SR (1993) Magnetic resonance imaging and localized in vivo proton spectroscopy in patients with fulminant hepatic failure. Amer J Gastroenterol 88:670–674

Häussinger D, Laubenberger J, Vom Dahl S, Ernst T, Bayer S, Langer M, Gerok W, Hennig J (1994) Proton magnetic resonance spectroscopy studies on human brain *myo*-inositol in hypoosmolarity and hepatic encephalopathy. Gastroenterology 107:1475–1480

Hedley-Whyte E, Hsu DW (1986) Effect of dexamethasone on blood–brain barrier in the normal mouse. Ann Neurol 19:373–377

Heng AE, Vacher P, Aublet-Cuvelier B, Garcier JM, Sapin V, Deteix P, Souweine B (2007) Centropontine myelinolysis after correction of hyponatremia: role of associated hypokalemia. Clin Nephrol 67:345–351

Hoheisel D, Nitz T, Franke H, Wegener J, Hakvoort A, Tilling T, Galla HJ (1998) Hydrocortisone reinforces the blood–brain barrier properties in a serum free cell culture system. Biochem Biophys Res Commun 244:312–316

Illowsky BP, Laureno R (1987) Encephalopathy and myelinolysis after rapid correction of hyponatraemia. Brain 110:855–867

Isaacks RE, Bender AS, Kim CY, Prieto NM, Norenberg MD (1994) Osmotic regulation of *myo*-inositol uptake in primary astrocyte cultures. Neurochem Res 19:331–338

Isaacks RE, Bender AS, Kim CY, Shi YF, Norenberg MD (1999a) Effect of ammonia and methionine sulfoximine on *myo*-inositol transport in cultured astrocytes. Neurochem Res 24:51–59

Isaacks RE, Bender AS, Kim CY, Shi YF, Norenberg MD (1999b) Effect of osmolality and anion channel inhibitors on *myo*-inositol efflux in cultured astrocytes. J Neurosci Res 57:866–871

Karp BI, Laureno R (2000) Central pontine and extrapontine myelinolysis after correction of hyponatremia. Neurologist 6:255–266

Ke QH, Liang TB, Yu J, Zheng SS (2006) A study of the pathogenesis and prevention of central pontine myelinolysis in a rat model. J Int Med Res 34:264–271

Kepes JJ, Reece CA, Oxley DK (1965) Central pontine myelinolysis in a 7-year-old boy. J Neurol Neurosurg Psychiat 28:39–47

Klavins JV (1963) Central pontine myelinolysis. J Neuropathol Exp Neurol 22:302–317

Kleinschmidt-DeMasters BK, Norenberg MD (1981) Rapid correction of hyponatremia causes demyelination: relation to central pontine myelinolysis. Science 211:1068–1070

Kleinschmidt-DeMasters BK, Rojiani AM, Filley CM (2006) Central and extrapontine myelinolysis: then...and now. J Neuropathol Exp Neurol 65:1–11

Kreis R, Ross BD, Farrow NA, Ackerman Z (1992) Metabolic disorders of the brain in chronic hepatic encephalopathy detected with H-1 MR spectroscopy. Radiology 182:19–27

Lampl C, Yazdi K (2002) Central pontine myelinolysis. Eur Neurol 47:3–10

Laureno R (1980) Experimental pontine and extrapontine myelinolysis. Ann Neurol 8:117

Laureno R (1983) Central pontine myelinolysis following rapid correction of hyponatremia. Ann Neurol 13:232–242

Leslie KO, Robertson AS, Norenberg MD (1980) Central pontine myelinolysis: an osmotic gradient hypothesis. J Neuropathol Exp Neurol 39:370

Lien Y-HH (1995) Role of organic osmolytes in myelinolysis. A topographic study in rats after rapid correction of hyponatremia. J Clin Invest 95:1579–1586

Lien Y-HH, Shapiro JI, Chan L (1991) Study of brain electrolytes and organic osmolytes during correction of chronic hyponatremia. Implications for the pathogenesis of central pontine myelinolysis. J Clin Invest 88:303–309

Liu JS, Zhao ML, Brosnan CF, Lee SC (2001) Expression of inducible nitric oxide synthase and nitrotyrosine in multiple sclerosis lesions. Am J Pathol 158:2057–2066

Lohr JW (1994) Osmotic demyelination syndrome following correction of hyponatremia: association with hypokalemia. Am J Med 96:408–413

Lubrich B, Spleiss O, Gebicke-Haerter PJ, Van Calker D (2000) Differential expression, activity and regulation of the sodium/myo-inositol cotransporter in astrocyte cultures from different regions of the rat brain. Neuropharmacology 39:680–690

Ludwin SK (1997) The pathobiology of the oligodendrocyte. J Neuropathol Exp Neurol 56:111–124

Martin RJ (2004) Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. J Neurol Neurosurg Psychiat 75(Suppl 3):iii22–iii28

McKee AC, Winkelman MD, Banker BQ (1988) Central pontine myelinolysis in severely burned patients: relationship to serum hyperosmolality. Neurology 38:1211–1217

Messert B, Orrison WW, Hawkins MJ, Quaglieri CE (1979) Central pontine myelinolysis. Considerations on etiology, diagnosis, and treatment. Neurology 29:147–160

Michell AW, Burn DJ, Reading PJ (2003) Central pontine myelinolysis temporally related to hypophosphataemia. J Neurol Neurosurg Psychiat 74:820

Monteiro L (1971) La myelinolyse du centre du pont dans cadre d'un nouveau syndrome histopathologique de topographie systematisee. J Neurol Sci 13:293–314

Murase T, Sugimura Y, Takefuji S, Oiso Y, Murata Y (2006) Mechanisms and therapy of osmotic demyelination. Am J Med 119:S69–S73

Neuwelt EA, Barnett PA, Bigner DD, Frenkel EP (1982) Effects of adrenal cortical steroids and osmotic blood–brain barrier opening on methotrexate delivery to gliomas in the rodent: the factor of the blood–brain barrier. Proc Natl Acad Sci USA 79:4420–4423

Norenberg MD (1981) Ultrastructural observations in electrolyte-induced myelinolysis. J Neuropathol Exp Neurol 40:319

Norenberg MD (1983) A hypothesis of osmotic endothelial injury. A pathogenetic mechanism in central pontine myelinolysis. Arch Neurol 40:66–69

Norenberg MD (1984) Treatment of hyponatremia: the case for a more conservative approach. In: Narins RG (ed) Controversies in nephrology and hypertension. Churchill Livingstone, New York, pp 379–391

Norenberg MD, Bell KP (1982) Plasminogen activator and steroids in electrolyte-induced myelinolysis. Proc Int Cong Neuropathol 9:76

Norenberg MD, Papendick RE (1984) Chronicity of hyponatremia as a factor in experimental myelinolysis. Ann Neurol 15:544–547

Norenberg MD, Leslie KO, Robertson AS (1982) Association between rise in serum sodium and central pontine myelinolysis. Ann Neurol 11:128–135

Oh MS, Choi KC, Uribarri J, Sher J, Rao C, Carroll HJ (1990) Prevention of myelinolysis in rats by dexamethasone or colchicine. Amer J Nephrol 10:158–161

Okeda R (1974) Centrale pontine Myelinolyse. Pathogetische Aspekte aufgrund morphometrischer Untersuchungen des Brückenfusses. Acta Neuropathol 27:233–246

Powers JM, McKeever PE (1976) Central pontine myelinolysis. An ultrastructural and elemental study. J Neurol Sci 29:65–81

Pujol J, Kulisevsky J, Moreno A, Deus J, Alonso J, Balanzó J, Martí-Vilalta JL, Capdevila A (1996) Neurospectroscopic alterations and globus pallidus hyperintensity as related magnetic resonance markers of reversible hepatic encephalopathy. Neurology 47:1526–1530

Qadir F, Hasan A, Masood M (2005) Extra pontine myelinolysis associated with hypophosphatemia. J Pakistan Med Assoc 55:254–256

Rapoport SI (1976) Blood–brain barrier in physiology and medicine. Raven, New York

Reynolds TB (1980) Water, electrolyte, and acid-base disorders in liver disease. In: Maxwell MH, Kleeman CR (eds) Clinical disorders of fluid and electrolyte metabolism. McGraw-Hill, New York, pp 1251–1261

Riggs JE, Schochet SS Jr (1989) Osmotic stress, osmotic myelinolysis, and oligodendrocyte topography. Arch Pathol Lab Med 113:1386–1388

Rojiani AM, Prineas JW, Cho ES (1987) Protective effect of steroids in electrolyte-induced demyelination. J Neuropathol Exp Neurol 46:495–504

Rojiani AM, Prineas JW, Cho E-S (1994a) Electrolyte-induced demyelination in rats—I. Role of the blood-barrier and edema. Acta Neuropathol 88:287–292

Rojiani AM, Cho E-S, Sharer L, Prineas JW (1994b) Electrolyte-induced demyelination in rats—II. Ultrastructural evolution. Acta Neuropathol 88:293–299

Rosenberg GA, Dencoff JE, Correa N Jr, Reiners M, Ford CC (1996) Effect of steroids on CSF matrix metalloproteinases in multiple sclerosis: relation to blood–brain barrier injury. Neurology 46:1626–1632

Rosman NP, Kakulas BA, Richardson EP Jr (1966) Central pontine myelinolysis in a child with leukemia. Arch Neurol 14:273–820

Schneck SA, Burks JS, Yarnell PR (1978) Antemortem diagnosis of central pontine myelinolysis. Neurology 28:389

Scolding NJ, Morgan BP, Houston A, Campbell AK, Linington C, Compston DA (1989) Normal rat serum cytotoxicity against syngeneic oligodendrocytes. Complement activation and attack in the absence of anti-myelin antibodies. J Neurol Sci 89:289–300

Shurtliff LF, Ajax ET, Englert E Jr, D'Agostino AN (1966) Central pontine myelinolysis and cirrhosis of the liver. A report of four cases. Am J Clin Pathol 46:239–244

Silver SM, Schroeder BM, Sterns RH, Rojiani AM (2006) Myoinositol administration improves survival and reduces myelinolysis after rapid correction of chronic hyponatremia in rats. J Neuropathol Exp Neurol 65:37–44

Simka M (2009) Blood brain barrier compromise with endothelial inflammation may lead to autoimmune loss of myelin during multiple sclerosis. Curr Neurovasc Res 6:132–139

Singh N, Yu VL, Gayowski T (1994) Central nervous system lesions in adult liver transplant recipients: clinical review with implications for management. Medicine 73:110–118

Sinton CM, Fitch TE, Petty F, Haley RW (2000) Stressful manipulations that elevate corticosterone reduce blood–brain barrier permeability to pyridostigmine in the rat. Toxicol Appl Pharmacol 165:99–105

Soupart A, Penninckx R, Stenuit A, Decaux G (2000) Azotemia (48 h) decreases the risk of brain damage in rats after correction of chronic hyponatremia. Brain Res 852:167–172

Soupart A, Silver S, Schroeder B, Sterns R, Decaux G (2002) Rapid (24-h) reaccumulation of brain organic osmolytes (particularly myo-inositol) in azotemic rats after correction of chronic hyponatremia. J Am Soc Nephrol 13:1433–1441

Starzl TE, Schneck SA, Mazzoni G, Aldrete JA, Porter KA, Schroter GP, Koep LJ, Putnam CW (1978) Acute neurological complications after liver transplantation with particular reference to intraoperative cerebral air embolus. Ann Surg 187:236–240

Sterns RH, Silver S, Kleinschmidt-DeMasters BK, Rojiani AM (2007) Current perspectives in the management of hyponatremia: prevention of CPM. Expert Rev Neurotherap 7:1791–1797

Strange K (1992) Regulation of solute and water balance and cell volume in the central nervous system. J Am Soc Nephrol 3:12–27

Strange K (1993) Maintenance of cell volume in the central nervous system. Pediatr Nephrol 7:689–697

Sugimura Y, Murase T, Takefuji S, Hayasaka S, Takagishi Y, Oiso Y, Murata Y (2005) Protective effect of dexamethasone on osmotic-induced demyelination in rats. Exp Neurol 192:178–183

Thurston JH, Hauhart RE, Nelson JS (1987) Adaptive decreases in amino acids (taurine in particular), creatine, and electrolytes prevent cerebral edema in chronically hyponatremic mice: rapid correction (experimental model of central pontine myelinolysis) causes dehydration and shrinkage of brain. Metab Brain Dis 2:223–241

Todd AS (1972) Endothelium and fibrinolysis. Atherosclerosis 15:137–140

Tomlinson BE, Pierides AM, Bradley WG (1976) Central pontine myelinolysis. Two cases with associated electrolyte disturbance. Quart J Med 45:373–386

Vadeboncoeur N, Segura M, Al Numani D, Vanier G, Gottschalk M (2003) Pro-inflammatory cytokine and chemokine release by human brain microvascular endothelial cells stimulated by Streptococcus suis serotype 2. FEMS Immunol Med Microbiol 35:49–58

Vanguri P, Koski CL, Silverman B, Shin ML (1982) Complement activation by isolated myelin: activation of the classical pathway in the absence of myelin-specific antibodies. Proc Natl Acad Sci USA 79:3290–3294

Verbalis JG, Gullans SR (1991) Hyponatremia causes large sustained reductions in brain content of multiple organic osmolytes in rats. Brain Res 567:274–282

Verbalis JG, Gullans SR (1993) Rapid correction of hyponatremia produces differential effects on brain osmolyte and electrolyte reaccumulation in rats. Brain Res 606:19–27

Verbalis JG, Martinez AJ (1991) Neurological and neuropathological sequelae of correction of chronic hyponatremia. Kidney Int 39:1274–1282

Verma S, Nakaoke R, Dohgu S, Banks WA (2006) Release of cytokines by brain endothelial cells: a polarized response to lipopolysaccharide. Brain Behavior Immun 20:449–455

Wing MG, Zajicek J, Seilly DJ, Compston DA, Lachmann PJ (1992) Oligodendrocytes lack glycolipid anchored proteins which protect them against complement lysis. Restoration of resistance to lysis by incorporation of CD59. Immunology 76:140–145

Wren DR, Noble M (1989) Oligodendrocytes and oligodendrocyte/type-2 astrocyte progenitor cells of adult rats are specifically susceptible to the lytic effects of complement in absence of antibody. Proc Natl Acad Sci USA 86:9025–9029

Wright DG, Laureno R, Victor M (1979) Pontine and extrapontine myelinolysis. Brain 102:361–385

Wszolek ZK, McComb RD, Pfeiffer RF, Steg RE, Wood RP, Shaw BW Jr, Markin RS (1989) Pontine and extrapontine myelinolysis following liver transplantation: relationship to serum sodium. Transplantation 48:1006–1012