Central and Extrapontine Myelinolysis: Then…and Now

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Abstract
In this review, we emphasize neuropathologic and neurobehavioral aspects of central pontine and extrapontine myelinolysis (CPM/EPM), also known as the osmotic demyelination syndrome. The literature is reviewed from the time of the initial report in 1959 and from key developments that have occurred more recently. Particular consideration is given to pathogenic mechanisms as revealed by recent animal studies. The role of white matter pathology in neurobehavioral dysfunction is also considered. The “then” and “now” of CPM and EPM tell 2 different stories. Yet, in many respects, this expansion of information over the past nearly 50 years simply represents a continuum, as well as recognition, of the vast gaps that still persist in our understanding of this disorder.

Key Words: Alcoholism, Central pontine myelinolysis, Extrapontine myelinolysis, Hyponatremia, Lateral pontine myelinolysis, Osmotic demyelination, Pathogenesis, White matter.

INTRODUCTION
Several excellent reviews have recently appeared in the internal medicine and neurology literature on central pontine and extrapontine myelinolysis (CPM/EPM), also known as osmotic demyelination syndrome, and have provided concise overviews on the topic from a clinical perspective. These studies have focused on historical aspects and updates on treatment of hyponatremia (1), refutation of the role of factors other than correction of hyponatremia in the causation of CPM (2), delineation of clinical features related to pontine and extrapontine lesions (3, 4), and changes in underlying medical disorders associated with CPM (5). A study of 44 patients with CPM published in 1999 documented a significantly more favorable clinical outcome than many earlier clinical studies had suggested (6). Most clinically symptomatic patients can be controlled such as aspiration pneumonia, septicemia, deep venous thromboses, and pulmonary emboli (6); in this study, one third of survivors recovered completely, one third had some deficits but were independent, and one third had more significant neurologic deficits (6). Several new etiologic mechanisms have been proposed for CPM/EPM, including apoptosis (7, 8). In this issue of the Journal of Neuropathology & Experimental Neurology, an original study describing the role of myoinositol and possible pathogenic osmotic mechanisms appears (9).

In the process of developing the content for this review, the question “can more be said on CPM/EPM?” was certainly raised. Although historical, clinical, and neuroradiologic perspectives have often been covered by others, certain issues still remain even within these categories. Neurobehavioral changes have rarely been discussed, and more recent considerations of possible pathogenic mechanisms merit further discussion.

Historical Aspects
Then…

The seminal paper of Adams et al from 1959 that first recognized CPM as a new disorder is familiar to most neuropathologists (10). Based on their puzzling clinical experience with 2 patients and detailed autopsy study of 2 additional asymptomatic cases identified from review of a 10-year period of autopsies at Massachusetts General Hospital, these authors identified a lesion of sharply outlined myelin loss that seemed to suffuse out from the midline, within the rostral, central pons (10). The strikingly unique features of CPM on detailed histologic examination indicated that the disease could hardly have been present, but otherwise overlooked, by earlier neuropathologists. The authors were “unable to discover any reference to a disease of this type in the medical literature of the past 75 years” (10).

The pontine involvement in all 4 cases was stereotypic in shape, location, and symmetry. The authors predicted that “the nature and location of the disease favor either an exogenous or an endogenous intoxication, or a deficiency of some essential substance” (10). Vascular diseases, Wernicke encephalopathy, Marchiafava-Bignami disease, and multiple sclerosis were all carefully considered, discussed, and excluded. Serum electrolyte abnormalities were not suspected in the original report because values were not routinely measured in those years (1950–1959). Instead, the original authors focused their attention on malnutrition (one of 4 of the original patients) or alcoholism (3 of the 4 original patients) as causative factors (10).
The Explosion of Central Pontine Myelinolysis Cases

Then...

CPM was recognized to be an iatrogenic disorder linked to the “plastic revolution” of the 1950s and the advent of widespread therapy with intravenous fluids (4). As testimony to the fact that something had been introduced into the routine practice of medicine that was related causally to CPM, the number of reported cases increased exponentially soon thereafter. By 1976, 150 examples had been cited (13), 315 as of 1985, and an additional 442 between 1986 and 2002 (5), with the obvious caveat that these only represented cases reported in the literature, not necessarily reflecting the true incidence of the disorder. The first association with electrolyte disturbances is usually credited to Finlayson et al (1973) (14) or Tomlinson and colleagues in 1976 (15). Lampl and Yazdi (5), however, cite Adams in 1962 (16) as having first mentioned hyponatremia in the context of CPM. Nevertheless, it was Norenberg and colleagues who provided some of the most convincing links between hyponatremia and CPM in 1977 (17) and again in 1982 (18) with detailed clinical studies.

By the early 1980s, the role of rapid correction of hyponatremia as causative of CPM-like lesions was established in dogs (19), rabbits (20), and rats (21). Uncorrected hyponatremia was excluded as causative of disease (1, 21). Despite these convincing studies, controversy persists because there remains a group of patients with CPM without hyponatremia or significant elevations in serum sodium, leading to speculation that other factors are involved.

…and Now

Although clinically symptomatic disease obviously takes precedence in patient care settings (and forms the basis for most reports in clinical journals), the presence of a condition such as CPM/EPM must be defined on a morphologic basis when trying to identify causative mechanisms. Based on autopsy findings and retrospective clinical correlation, it has been well recognized that many, if not the majority, of CPM cases are clinically asymptomatic. Indeed, 2 of the 4 original patients reported by Adams et al had no symptoms referable to their lesions, a feature the original authors found completely unsurprising because in these 2 patients, the lesion was small and located in the midline and hence involved too few critical lateral corticospinal/corticobulbar tracts or tegmental structures to produce obvious clinical signs (10). Slager, in 1986, reported 21 cases of CPM in a series of 220 consecutive autopsies on patients with chronic liver disease, none of whom were symptomatic; hence, all CPM cases, even in this highly vulnerable population seen at a major medical center, were clinically unrecognized (22). This paper again underscored the role of the autopsy in making the diagnosis of CPM/EPM. In our own experience 10 years later, careful review at autopsy of 3,247 brains (with particular attention paid to examination of the pons) disclosed 15 cases of CPM (overall incidence of 0.5%) in only one of whom was the diagnosis of CPM even considered premortem (23).

The statement has been made by some clinicians that they have never had a patient develop CPM after rapid correction of hyponatremia despite this still being the best documented etiologic factor associated with CPM development (24). Clinical signs of CPM/EPM are often obscured in critically ill patients with multiorgan failure and/or hepatic encephalopathy (1). However, the small size and sparing of critical structures such as corticobulbar and corticospinal tracts in many CPM cases makes it unlikely that small lesions would produce clinical features. This point is supported by one of our clinically undetected cases with a small, CPM lesion (Fig. 1C) and case no. 3 of Adams et al (10), which also had a very small lesion. Occasionally, neuroimaging may detect these asymptomatic (25) or mild (26) CPM cases.

An observation we have made recently in our own autopsy neuropathology practice is that clinically recognized CPM/EPM cases may actually be on the rise. We speculated (and hoped) in 1996 that perhaps changes in electrolyte management practices had favorably contributed to our finding only clinically unsuspected, small incidental cases at autopsy at our institution during the 12 years of the study from 1983 through 1994 (23). Since 2000, we have encountered 7 cases at autopsy, several of which had clinically diagnosed or suspected CPM, large pontine lesions, and large incremental rises in their serum sodium as a result of therapeutic intervention (Table). The emphasis in the clinical literature on the ability of clinicians to safely increase serum sodium without causing CPM/EPM may have imparted a false sense of confidence. Stated another way, although perhaps some patients can tolerate a relatively rapid iatrogenic rise in serum sodium, some cannot, and to date, we do not fully understand the concomitant osmolar and water balance issues in this subset of patients.
The Role of Underlying Disease in the Pathogenesis of Central Pontine Myelinolysis

Then...

From the time of the initial report, virtually all cases of CPM were recognized to occur in the setting of concomitant chronic diseases, and chronicling these conditions has occupied much of the literature on CPM/EPM. Before 1985, the incidence of coassociated disorders in reported cases included chronic alcoholism (41%), electrolyte disturbances (hyponatremia or hypernatremia; 32%), pulmonary infections (10%), malignant tumors (6%), and diseases of the central nervous system (hemorrhages, tumors, trauma, and so on; 7%) (5). After the advent of liver transplantation, a shift...
took place in the incidence of the various diseases that underlie CPM (5).

…and Now

Although chronic alcoholism as a coassociated risk factor has remained unchanged (39% of reported cases) in the years after 1986, well-documented correction of hyponatremia now has been identified in 21.5% of reports and represents the second most frequent condition coassociated with CPM. Hyponatremia may be the result of hepatic cirrhosis, infusion treatment, drugs, and especially the syndrome of inappropriate antidiuretic hormone, with the latter accounting for many cases attributed to pulmonary and intestinal tract malignant tumors, as well as CNS tumors, encephalitis, trauma and bleeding, and pulmonary infections (5). Hyponatremia has recently been recorded secondary to cerebral salt wasting syndrome after pituitary surgery (27).

Since 1986, 17% of reported CPM cases have been attributed to liver transplantation, making this the most third common coassociated condition after chronic alcoholism and correction of hyponatremia (5). CPM appears particularly likely to occur within the first 30 days after transplantation (28). Several large series on liver transplant recipients have also linked CPM with hyponatremia or wide variations in serum sodium preceding the onset of the disorder (29–31). Important determinants in liver transplant recipients are additionally cited by some authors to be sepsis, metabolic disorders, hepatic encephalopathy, hypoxia, and cyclosporine or tacrolimus treatment (32). However, as noted by Karp and Launois, many factors in patients with hepatic disease are likely to be occurring in the same vulnerable population but are not causally related (2). This is particularly true for cyclosporine and tacrolimus, which cause a white matter disorder similar to reversible posterior leukoencephalopathy (33) that could be confused with the EPM lesions seen in CPM (2).

A number of recent reports have focused on documenting less common underlying disorders, hoping to further identify an elusive additional factor(s) that might predispose patients to CPM/EPM development. Patients with burns (34), acquired immunodeficiency syndrome (35), and hyperemesis gravidarum have developed CPM (5). Single cases of CPM in infants (36), central nervous system Sjögren syndrome (37), systemic lupus erythematosus (38), acute intermittent porphyria (39), cytomegalovirus hepatitis (40), Epstein Barr virus-associated hemophagocytic syndrome (41), anaphylactic shock (42), and heat stroke (43) have all been reported in the past 8 years. CPM remains rare in most of these conditions, except possibly for burn patients, in whom up to 7% of burn patients were reported to have the disorder (34).

Other Possible Risk Factors and Cofactors: The Role of Other Osmotic Derangements

It has always been recognized that although serum sodium is the main determinant of serum osmolality, a complex equation determines the final picture.

Then…

Adams et al originally recognized a possible role for hypokalemia in the etiology of CPM based on the presence of abnormalities in the electrocardiogram in one of their 4 patients even before abnormalities in serum sodium were linked to the disease (10). Hypokalemia has been cited in individual papers over the years by several workers (44–47). Diabetic ketoacidosis may result in marked shifts in osmolarity, which also make patients more susceptible to development of CPM (48). CPM occurring in the setting of hypernatremia and hyperglycemia in the absence of hyponatremia has been documented a number of times, as reviewed by McComb et al (49).

Riggs and Schochet reported a patient who developed CPM in the setting of acute hemorrhagic pancreatitis and moderate sustained serum hyperosmolality but without hyponatremia or elevation in serum sodium (50). Cases such as this suggest that although osmotic stress in the majority of patients is the result of serum sodium alterations, in rare instances, other causes of osmotic aberrations may cause disease. This recognition subsequently led to adaptation of the term CPM to “osmotic demyelination syndrome” by these same authors (50).

FIGURE 1. (A) A 1932 example of central pontine myelinolysis (CPM) reproduced from a German-language article by Luthy on hepatocerebral degeneration (Luthy F. Uber die hepato-lentikulare degeneration. Deutsche Zeitschrift fur Nervenheilkunde 1932;123:101–56; used with permission from Springer Verlag). Myelin stain. (B) This typical example of chronic active CPM with early cavitation demonstrates the well-demarcated, batwing area of myelin loss suffusing out from the midline at the level of the fifth cranial nerve. This case is taken from our files and nicely parallels the historical example seen in (A). Whole-mount section stained with Luxol fast blue-periodic acid Schiff stain for myelin. (C) In contrast to the large typical example in (B), small CPM lesions such as this one may be easily overlooked grossly and even microscopically, particularly if they are subacute and not yet cavitated, as in this example. Small lesions such as this one would not be expected to produce clinical symptoms, and this case was discovered only at autopsy. Whole-mount section stained with Luxol fast blue-periodic acid Schiff stain for myelin. (D, E) This pair of corresponding gross (D) and whole-mount sections (E) from the same patient with a subacute CPM lesion come from a patient who was diagnosed with CPM pre-mortem. Patient 2 in the Table is illustrated. (E) Whole-mount section stained with Luxol fast blue-periodic acid Schiff stain for myelin. (F, G) The most difficult lesions to recognize grossly and microscopically are those in lateral pontine (F, patient 3 in the Table is illustrated; most subtle areas circled) and extrapontine (patient 2 in the Table is illustrated) sites. The lateral geniculate is one of the most frequently, and often the only, extrapontine site involved in a case (G, arrow). (H) All 3 of our acute or subacute examples of CPM showed axonal swellings within their lesions. Modified Bielschowsky stain for axons, 600×. (Pontine lesion from patient 2 in the Table is illustrated.) (I) Occasionally, large lesions may be associated with a mild perivascular lymphocytic infiltrate, which does not negate the diagnosis of CPM. These lymphocytes are usually T cells and may represent a response to extensive tissue injury. Hematoxylin and eosin, 600×. (Lesion from patient 4 from the Table with active CPM is illustrated.)
and Now

Most recently, hemodialysis, with its alterations in blood chemistries, osmolality, and shifts in urea from the extracellular fluid, has been associated with CPM-like lesions in pontine and extrapontine sites (51). These may resolve rapidly, favoring transient edema rather than completed structural damage to myelin sheaths (51).

Folate depletion (52) and hypophosphatemia (53, 54) have also been cited as cofactors. Administration of drugs (diuretics, cytostatics, antidiabetics, antidepressants, barbiturates, clofibrate) (5), parenteral magnesium administration (55), fatal overdose of arginine hydrochloride (56), and lithium toxicity have all been reported as precipitating events and are examples of when the disease occurs in otherwise healthy patients. The role of other factors affecting the brain’s response to the hyponatremic state and its correction have been explored more recently with particular emphasis on organic substances such as myoinositol (9).

### Central Pontine and Extrapontine Topography

Then...

The original description of the disease entailed a single, symmetric, sharply outlined lesion confined to the center of the pons and hence led to the appellation “central pontine myelinolysis” (10). The lesion was centered on the median raphe and seemed to spread out from this midline area with relative sparing of the corticospinal and corticobulbar tracts of the basis pontis; tegmentum was affected only in the largest lesions.
Although large older lesions are relatively easy to identify at the time of gross examination of the pons, smaller lesions require close scrutiny and a high index of suspicion (Fig. 1C). Recent lesions may also be quite subtle, as illustrated by the matching gross (Fig. 1D) and whole-mount Luxol fast blue-periodic acid Schiff-stained section (Fig. 1E) from the same patient with subacute CPM. Even within the pons, lateral pontine lesions may be subtle (Fig. 1F). Extrapontine lesions are not easily identified grossly or microscopically (Fig. 1G). Hence, we routinely (blindly) submit multiple sections of pons and other sites of known EPM such as the lateral geniculate nucleus (Fig. 1G) in patients from high-risk groups or in patients with premortem aberrations in serum sodium values or osmolality.

…and Now

Within a few years, it became apparent, however, that CPM lesions could occur outside the pons. Lesions can extend up into the midbrain (but rarely down into medulla) and extrapontine lesions have been increasingly documented (4, 11). Cerebellum (33% of cases) and lateral geniculate body (30%) (Fig. 1G) (57) are the most frequently affected EPM sites, followed by external and extreme capsules, hippocampus, putamen, cerebral cortex/subcortex, thalamus, and caudate nucleus (4, 58). Unusual sites for EPM include spinal cord, mamillary bodies, columns of the fornix, amygdala, anterior commissure, optic tract, and subthalamic nucleus (4, 11, 58). It was originally believed that EPM rarely occurred without CPM but this has been refuted by the studies of Gocht and Colmant (58) and others (59, 60). Gocht and Comant found that extrapontine lesions were exclusively seen in 13 of their 58 myelinolysis cases, a number almost equivalent to the 18 of 58 cases affected by both CPM and EPM (58). Approximately half of their cases (27 of 58) had CPM alone (58). Given the difficulty of visualizing all but the midline, classic, large, batwing CPM lesions at the time of gross brain examination, EPM-only cases are more likely to go unrecognized.

Interestingly, despite the frequency of EPM, noncentral pontine lesions involving exclusively the lateral pons have been rarely recorded. One of the best-documented cases occurred in a patient with hyperglycemia and hypernatremia (49). Gocht and Colmant also included a patient with both lateral and central pontine lesions in their series (58). It is unclear what accounts for the development of lateral versus central pontine lesions. A clinical study of hyponatremic encephalopathy from 1992 showed no instances of CPM in the 20 patients studied by neuroimaging but identified 2 examples of lateral pontine lesions (61). Three fourths of patients also had diffuse cerebral lesions that the authors ascribed to anoxic ischemic rarefaction (64). Thus, although neuroimaging techniques have enhanced the likelihood of detecting pontine lesions, the specific diagnosis of CPM is still determined at postmortem examination.

Histopathology of Human and Experimental Lesions

Then…

Microscopically, within the area of demyelination, almost all of the features were beautifully detailed by the original authors, who noted that oligodendrocytes were lost, axons and nerve cells were spared except at the very center, blood vessels were unaffected, and inflammation was absent (10). Because of the gross and microscopic findings, CPM lesions were recognized as being distinct from infarcts and from inflammatory demyelinative lesions such as multiple sclerosis or acute disseminated encephalomyelitis, mostly as a result of absence of a lymphocytic infiltration (11).

…and Now

Detailed microscopic descriptions of pathology and lesion evolution in experimental models have been defined (21, 65–67). These descriptions are almost identical in most respects to the human disorder. Studies on the blood–brain barrier in rats, based on the initial hypothesis of osmotic injury of endothelial cells proposed by Norenberg (68), revealed an early opening of the blood–brain barrier. This was seen by leakage of peroxidase as early as 3 hours after the administration of hypertonic saline (66). This disruption of the blood–brain barrier was evident in the same areas where lesions typically developed. Additionally, increased pinocytotic activity was also observed, suggesting active transport of fluid across the endothelial cell. The histologic changes to the blood–brain barrier, however, were reversible, and evidence of permanent endothelial damage was not seen at later time points. Ultrastructurally, the presence of intracellular/intramyelinic edema is documented along with subsequent vasoergic edema (67). Swelling of the myelin sheath is followed by oligodendrocyte degeneration. This early damage initiates a cascade of events, including activation of microglia and active conversion to lipid-laden macrophages, the latter...
representing the end stage lesion. At this stage, some degree of endothelial hyperplasia and neovascularization may also be present. The increased cellularity described in both human and experimental lesions likely represents this enhanced reactive component, although lymphocyte infiltration is absent or minimal at best.

It must be noted, however, that although there is a clear lack of lymphocytes in the lesions, this does not preclude an inflammatory component to the development of lesions. Describing the effects of steroids on development lesions, Rojiani et al (65) detailed 3 histologic types of lesions: spongy, vacuolar and reactive, or hypercellular. The spongy lesions were felt to represent early demyelination. As the lesions evolved, there was an influx of microglia as well as increased vascular proliferation, yielding the reactive lesion. On the other hand, animals treated with steroids typically developed vacuolation in areas commonly developing demyelinating lesions such as the external capsule and pencil fibers of the basal ganglia. It was proposed that the initial spongy lesion required microglial activation to progress to the more severe reactive stage, whereas absence of microglia (as with steroid or colchicine treatment) yielded more vacuolated lesions (65, 69, 70). Preliminary studies in our laboratory with the same animal model have shown a marked decrease in glial fibrillary acidic protein (GFAP) immunoexpression in lesion areas. This depletion of GFAP coincides with an appearance of activated microglia as evidenced by lectin (griffon sia simplifolia B4) staining (71). Similar changes have been described in astrocyte cultures after addition of cytokines such as interleukin-1β (IL-1β) (72). Based on these and earlier observations, it appears that in this model, although blood–brain barrier opening constitutes the initial injury, it is microglia activity and subsequent cytokine release that accentuates myelin damage (65, 71).

An additional point about the microscopic features of CPM/EPM is that axonal damage and axonal swellings can be seen in acute/subacute cases (13) (Fig. 1H), and this finding may have therapeutic implications for early treatment of severe, clinically recognized CPM cases. Although Adams et al found no inflammation in their cases, it should be remembered that 2 cases were remote and the other 2 patients died on days 22 and 39 with well-advanced disease (9). Rarely, scant perivascular lymphocytic cuffing can be identified (11), shown here in an EPM site (Fig. 1I). Given the infrequency with which we have seen this microscopic feature, any inflammation in CPM/EPM cases must be very transient or seldom present and does not negate the diagnosis of CPM/EPM.

Clinical Symptoms Associated With Central Pontine and Extrapontine Myelinolysis

Then…

The original description of the clinical features of CPM in 1959 (10) remains instructive today. Classically, several hours to days after recovery from hyponatremia, affected patients experience the abrupt onset of encephalopathy (4, 10). An acute confusional state develops after an initial period of improvement, presumably related to the osmotic demyelination in the basis pontis. Other features may include pseudobulbar affect, stupor, and coma, and occasionally the locked-in syndrome may be seen. These disturbances are intermingled with other features of the disease, including the prominent motor manifestations of flaccid evolving to spastic quadriplegia, dysarthria, and dysphagia (4).

…and Now

CPM/EPM has been recognized as a prominent neurobehavioral disorder related to white matter disease in the pons and throughout the brain. There are no large series of patients with CPM studied cognitively, but several case reports have provided more detailed information for this disease. Detailed reports describe a diverse range of neuropsychiatric disorders, 2 with “behavioral change” (73, 74), one with “cognitive and emotional dysfunction” (75), one with impaired comportment (76), and one with catatonia (77). Clinical features include restlessness, emotional lability, apathy, akinetic mutism, agitation, insomnia, paranoia, delusions, rage, and disinhibition. Behavioral problems in the recovery period may be highly disruptive, but typically improvement occurs in those who survive the illness. Many of the clinical neurobehavioral features suggest a disturbance of frontal systems.

Neuropsychologic testing has been only rarely employed in the evaluation of patients with CPM. Three case reports include comprehensive neuropsychological testing (75, 78, 79), one with serial examinations 1 week after sodium correction and then again 4 months later (78). In general, IQ is mildly affected, information processing speed and attention are impaired, language is relatively spared, memory is poor (with a pattern suggesting prominent retrieval dysfunction), and executive function is disturbed (75, 78, 79). Cognitive recovery is observable but may be incomplete (78). The limited available information indicates that the cognitive profile in these cases is more reminiscent of white matter dementia than a cortical dementia such as Alzheimer disease (80).

The management of neurobehavioral deficits in affected patients can be challenging. Treatment of primary medical problems is the first priority, because many individuals have severe hepatic and other organ involvement that can exacerbate the encephalopathy related to CPM. Vigorous rehabilitation is crucial, as tolerated, to ensure optimal physical recovery. Although the symptomatic treatment of acute confusional state is complex and unstandardized, the use of atypical antipsychotic medications at low doses and for limited duration may be helpful in controlling behavioral disruption. One intriguing report noted improvement in mood, affect, motivation, and gait with methylphenidate (81), suggesting that arousal and attentional systems may be usefully engaged by appropriate stimulant medication.

The origin of the neurobehavioral deficits in CPM remains uncertain. Because it is now well known that CPM is accompanied by EPM in many cases (4), lesions both within the pons and elsewhere in the brain may be important. The pontine involvement clearly implies that arousal systems in the ascending reticular activating system are affected, and this localization may cause interference with the cortical and thalamic supply of serotonin, acetylcholine, and norepinephrine (73). The resulting syndrome of disinhibition and other
similar deficits could thus reflect the selective disruption of arousal, attentional, and frontal systems.

Although the brainstem has not traditionally been considered a major contributor to neurobehavioral status, such a hypothesis is plausible given the close proximity of many neurotransmitter systems whose nuclei originate in this region. In one of the cases described here, myelolysis confined to thepons was associated with both cognitive and behavioral dysfunction, as documented by neuropsychological testing (75). A selective frontal systems disturbance was suggested by prominent cognitive deficits in speed of information processing, attention, memory, and executive function, and behavioral deficits, including pathologic crying and laughter and emotional lability (75). Supportive evidence for the role of the brainstem in cognition has also been presented by van Zandvoort and colleagues (82), who studied a group of 17 patients with a single brainstem white matter lacunar infarct and found mild but significant impairment on selected tests (e.g. Boston Naming Test, category fluency, and trail-making) that were similar to the deficits encountered with supratentorial white matter lacunes. Isolated pontine white matter lesions of CPM may produce similar neurobehavioral effects.

The role of EPM in neurobehavioral dysfunction is still more puzzling. Extrapontine lesions may also contribute to the frontal systems disturbance suggested by the clinical profile of these patients. One case documents the association of CPM with Marchiafava-Bignami disease (77); the similarity of these diseases was first noted by Adams and colleagues in 1959 (10). It is not clear, however, that CPM and Marchiafava-Bignami disease have any relationship other than by chance. Of more interest may be the involvement of the U (arcuate) fibers that has been recently noted. U fibers are short association fibers that connect adjacent cortical gyri, and although it is generally assumed that they participate in higher functions, their exact role is obscure. In CPM/EPM, a contribution to neurobehavioral dysfunction is conceivable with U fiber damage. By analogy, other disease states may shed light on this issue. Paskavitz and colleagues (83) described acute mania and encephalopathy in a patient with Epstein-Barr virus-related ADEM of the arcuate fibers. Miki et al (84) studied 53 patients with multiple sclerosis with similar white matter lesion volumes and found that 8 patients with multiple isolated U fiber lesions had significantly greater executive control and memory dysfunction than 45 patients with none or a single U fiber lesion.

Pathogenic Considerations

Considerations of etiopathogenic mechanisms must be based on an understanding of morphologic correlates, pathologic manifestations, and functional alterations, which together yield a coherent and plausible explanation. Notwithstanding this desire to find such an answer, most proposed mechanisms fall short in one aspect or another. A question that still begs to be answered is “Why do many patients who undergo correction of hyponatremia fail to develop CPM?” Conversely, case reports have appeared, both then and now, citing instances in which CPM developed despite careful correction of hyponatremia (85–88) or in normonatremic patients (89). One critical determinant in this context appears to be the chronic nature of the predisposing condition and the acute nature of its correction.

Then…

Norenberg and Papendick in 1984 studied a group of rats that were hyponatremic for 1 day versus a second group that had been maintained in a hyponatremic state for 3 days before administration of hypertonic saline (90). The 3-day hyponatremic rats developed more numerous and severe demyelinating lesions (90). This, and clinical observational studies, have led to the recommendation that a distinction should be made, whenever possible, between acute and chronic hyponatremia with correction at different rates. The recommendation is that acute hyponatremia can be corrected at a minimum rate of 1 mmol/L per hour, but chronic hyponatremia should be corrected at less than 0.5 mmol/L per hour (5).

…and Now

Although the recommendations outlined here remain the most significant, albeit sometimes controversial clinical intervention in this context, additional considerations have emerged that may impact our understanding of the etiology of CPM and its evolution. The issue of inflammation in CPM/EPM is an interesting one, given the fact that several groups are attempting to develop effective antiapoptotic drugs in addition to minocycline, which might be of therapeutic benefit in any central nervous system disease with an inflammatory component. The initial studies that steroids administered just before rapid correction of chronic hyponatremia have a protective effect in rats, decreasing the incidence and severity of lesions, merits clinical translation in severely symptomatic hyponatremic patients (65). Proposed mechanisms included stabilization of the blood–brain barrier and suppression of microglia-derived cytokines. These studies were predicated by the hypothesis of osmotic endothelial injury proposed by Norenberg and Papendick (90).

Recently, Ashrafian and Davey have argued that CPM is multifactorial and is only likely to occur in patients with conditions that predispose to deficiencies in neuronal and glial energy supply (7). They note that even patients with mild hyponatremia or “gentle correction of hyponatremia” can develop CPM if the electrolyte problems occur on a background of energy deprivation states such as chronic alcoholism or liver disease. These authors reasoned that alcoholic or cirrhotic patients, as well as patients with hypoglycemia from other causes (91–93), may lack a sufficient reserve supply of glucose or glycogen to furnish glial cells with the energy necessary to maintain Na⁺-K⁺ ATPase pump activity, the mechanism responsible for electron transport in the brain. Subclinical thiamine deficiency may also exacerbate the problem because it decreases brain glucose uptake and further diminishes available energy sources for glial cells. Neurons may release glutamate and other excitatory molecules in response to the osmotic stress, altering calcium channels and increasing intracellular calcium content. The latter is a known...
stimulus to apoptotic cell death, which these authors postulate may be the ultimate mechanism for CPM (7).

Finally, in this issue of the Journal of Neuropathology & Experimental Neurology, Silver et al (9) address the role of organic osmolytes and myoinositol in particular in the correction of chronic hyponatremia. The brain has a well-developed osmoregulatory mechanism that responds in an adaptive manner to prevent alterations in cell volume. Thus, in situations of osmotic change such as chronic hyponatremia, if the brain must choose between changes in cellular volume versus changes in osmolality, volume is preserved. Changes in intracellular osmolality are an adaptive function and result from an increase or loss of osmolar particles. When dealing with hyponatremia, the correction is affected by loss of not only electrolytes, but also organic osmolytes including amino acids (alanine, glutamine, glutamate, taurine, and glycine) and sugars such as myoinositol. During stages of chronic hyponatremia, preservation of cell volume mandates loss of these osmolytes. However, during rapid correction of hyponatremia, intracellular electrolyte corrections are rapid but the brain is unable to correct the lost organic osmolytes expeditiously, resulting in cell injury and demyelination (94–96). The study reports the protective effect of myoinositol administration in preventing demyelination after correction of chronic hyponatremia. In the final analysis, the “then” and “now” of CPM and EPM tell 2 different stories. Yet, in many respects, this article is dedicated to Dr. Michael Norenberg, whose work particularly on CPM inspired our careers. The authors thank Ms. Susan Peth for expert manuscript preparation and Ms. Lisa Litzenberger for photographic assistance.

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