Central Pontine Myelinolysis

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Key Words

Central pontine myelinolysis • Extrapontine myelinolysis • Osmotic endothelial injury • Osmotic dysmyelination • Hyponatraemia

Abstract

In 1949, Victor and Adams observed an alcoholic patient who developed quadriplegia and pseudobulbar palsy, and inability to chew, talk or swallow. A post-mortem confirmed their suspicion of 'a large, symmetrical, essentially demyelinating lesion occupying the greater part of the basis pontis.' This paper follows the historical evolution of central pontine myelinolysis and the changing concepts of its metabolic aetiology. Too rapid a rate of correction of hyponatraemia is the most common, but not invariable aetiology.

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Over 50 years ago, in 1949, a 38-year-old man with delirium tremens and pneumonia was admitted to Boston City Hospital, Massachusetts, under the care of Maurice Victor and Raymond Adams. Ten days after admission, they observed:

'a rapidly developing quadriplegia and pseudobulbar palsy, ... inability to chew, talk or swallow, but sparing of pupillary reflexes, eye movements, corneal reflexes and facial sensation' [1].

Victor and Adams suspected pathology in the basis pontis, which they argued on clinical grounds was unlikely to be an infarct or haemorrhage in a young man.

Their patient had no segmental brain stem signs, and his signs were too limited for a basilar occlusion. Twenty-two days after admission he died. The post-mortem showed:

'a large, symmetrical, essentially demyelinating lesion occupying the greater part of the basis pontis.

Over the next five years we had the opportunity to study three other cases pathologically and in 1959 these four cases were reported under the heading of central pontine myelinolysis' [1, 2].

Each case demonstrated a bilaterally symmetrical pontine myelin destruction with relative sparing of neurons and axons, inconsistent with infarction. This paper was the first comprehensive clinical account with pathological proof of central pontine myelinolysis (CPM). We may wonder what misdiagnoses concealed previous cases.

Adams and Victor [2] suspected a metabolic cause related to nutritional deficiency because all 4 of their patients were malnourished or alcoholic, and they noted: 'its invariable association with other serious or life threatening disease.' Subsequently this has been confirmed with about 40% cases related to alcoholism and several related to malnutrition and liver transplantation (table 1). Pathological similarities to alcohol-related Marchiafava-Bignami disease¹ are documented and Wernicke's encephalopathy is associated in up to 30% in pathological series. The salient symptoms are fits, stupor, coma and

¹ Marchiafava E, Bignami A: Sopra un'alterazione del corpo calloso osservata da soggetti alcoolisti. Riv Patol Nerv Ment 1903;8:544–549.

Fig. 1. CPM MRI: T₁ abnormal signal in the basis pontis. Courtesy of Timothy C. Hain, MD.

dementia, caused by demyelination of the corpus callosum, and cortical laminar necrosis involving the frontal and temporal lobes. Instances of related myelinolysis in the cerebral white matter have led to the term extrapontine myelinolysis [3].

In the majority of patients with pathologically demonstrated CPM there are no symptoms or signs that betray the pontine lesion, either because it is so small (2–3 mm) or because the coma of the associated illness masks the pontine pathology [2]. More severe cases show the characteristic quadriparesis, pseudobulbar palsy and locked-in syndrome. Mutism, parkinsonism, catatonia, and dys-tonia are also reported.

Brain MRI increases the diagnostic yield and shows hyperintense lesions on T₂-weighted, and hypointense lesions on T₁-weighted images, with no contrast enhancement in the central pons, and sparing of the tegmentum and ventrolateral pons (fig. 1) [4]. The lesion is often triangular on axial images and has a 'bat's wing' configuration in coronal images.

Osmotic Dysmyelination

The unravelling of the aetiology is an interesting trail of detection and experiment. The importance of serum sodium levels was not recognized until 1976, when in a crucial paper, Tomlinson et al. [5] from Newcastle upon Tyne noted:

Table 1. Disorders associated with CPM and extrapontine myelinolysis

Frequent causes	Rarer causes
Alcoholism	Psychogenic polydipsia
Malnutrition	Burns (infrequent, often with hypernatraemia)
	After pituitary surgery
	Post-uological/gynaecological surgery
	Prolonged diuretics
	After liver transplant

'Two patients with central pontine myelinolysis are described. Both were middle aged women presenting with a history of protracted vomiting and drowsiness. Hyponatraemia (serum sodium 96–100 mmol/l) was a feature in both patients. No underlying malignancy, alcoholism, malnutrition or other serious disease was identified. Correction of electrolyte abnormalities was accompanied by deterioration in level of consciousness and development of a neurological syndrome characterized by quadriparesis, dysphasia and mutism. Death followed and histopathological examination confirmed classical myelinolysis in the central pons and extensive similar, though not identical, lesions in the cerebral hemispheres in both cases. The pathophysiological basis of the lesions is likely to be a special metabolic susceptibility of oligodendroglial cells in areas where neurones, glial cells and myelin sheaths lie in close proximity to one another.'

Further cases confirmed the relation of CPM with hyponatraemia [6]; however, Laureno and Karp [7] confirmed the suspicion of Tomlinson et al. [5] that it was not hyponatraemia per se, but its correction, which was the essential pathogenesis. Wright et al. [3] had previously observed a patient with pontine and extrapontine myelinolysis at the Cleveland Metropolitan General Hospital, who had presented with confusion and severe hyponatraemia. Hypertonic saline treatment increased her sodium from 109 to 136 mmol/l over 18 h. However, she then deteriorated within days of treatment, and she became comatose and quadriplegic. At autopsy they found CPM and symmetrical extrapontine myelinolysis bilaterally in the thalamus, cerebellum, cortical and subcortical regions, and lateral geniculate body [8].

Laureno and colleagues [9] experimented on dogs that they rendered hyponatraemic by administration of vasopressin and intraperitoneal water. After several days of severe hyponatraemia, it was corrected by infusion of hypertonic saline and discontinuation of water and vasopressin. Initially the dogs improved, but within 48 h after normalization of the serum sodium the animals became paralyzed; at autopsy, symmetrical myelinolysis was evi-

dent in the middle of the pons, thalamocapsular regions, and in subcortical white matter. Thus, the experimental model successfully duplicated the clinical and pathologic features of human myelinolysis [7, 8] and the alternative name evolved: *osmotic dysmyelination* [10]. Confusingly, normonatremic, hypernatremic, and hypokalaemic patients have also subsequently been described [11]. Careful correction of acute hyponatraemia is generally devoid of sequelae. CPM is more characteristic of correction of chronic (>48 h) hyponatraemic states; however, there is no definite safe rate of correction.

The speculative mechanism is complicated by investigations that showed that myelinolysis did not occur in animals when serum sodium was gradually increased, nor with uncorrected hyponatraemia, nor in normonatremic dogs infused with hypertonic saline. Similar experiments in rats and rabbits [12] confirmed these results.

In man, CPM typically occurs when correction of the serum sodium level exceeds 12 mEq/l/day, but can occur in mild hyponatraemia with slower rates of correction. In rats, massive accumulations of microglia were observed that expressed the pro-inflammatory cytokines TNF- α and IFN- γ as well as inducible nitric oxide synthase. Lovastatin, which inhibits microglial infiltration, significantly reduces both neurological impairments and demyelination [13]. The mechanism of myelin loss in CPM is still poorly understood. One suggestion is that the increase in serum sodium produces an osmotic endothelial injury that releases myelinotoxic factors and initiates vasogenic oedema and apoptosis [14]. Intracellular osmolytes², measured by proton MR spectroscopy, are dramatically reduced under hyposmolar stress, and increased by hyperosmolality [15, 16].

Prognosis

Of the 34 patients for whom follow-up data were available, 32 survived. Of these, 11 completely recovered, 11 had some deficits but were independent, and 10 were dependent (4 through disorders of memory or cognition, 3 with tetraparesis, 2 with cerebellar ataxia, 1 with polyneuropathy). The outcome did not relate to the severity of the acute neurological deficits nor the degree of hypo-

natremia, or MRI changes [17]. The morbidity and mortality of CPM/extrapontine myelinolysis have been reduced by recognition of predisposing conditions, early diagnosis, modern neuroimaging, and cautious intensive treatment [18].

Treatment of Hyponatraemia

The problem occurs in those with chronic (>48 h) hyponatraemia and hypovolaemia, since the rise in plasma sodium caused by the administration of 0.9% saline is complicated by diuresis and free water loss caused by the reduction in hypovolaemia-induced ADH secretion.

In acute hyponatraemia, the urinary sodium is often >40 mmol/l, and plasma urea is low; in chronic hyponatraemia, the urinary sodium is usually <20 mmol/l, and plasma urea is often high. After correction of any contributing thiamine deficiency and hypokalaemia, water restriction alone should be started in milder cases. If unsuccessful, hypovolaemic subjects should receive intravenous isotonic saline (initially 1 litre may suffice). Currently, it is recommended that the increase in plasma sodium should be no greater than 8 mmol/l/24 h. Only in severe hyponatraemia should sodium chloride 1.8% cautiously be used [19].

Conclusion

The prediction of Adams et al. [1] that CPM has a metabolic cause has been amply justified. 'New diseases' are uncommon, and as in this instance may reflect the lack of relevant techniques of investigation rather than lack of observation at the bedside. Before the report by Adams et al. [1], many cases may have been overlooked because serum sodium was not routinely performed in medical or surgical wards. Thus, the nexus between fluctuating serum sodium and myelinolysis was not apparent.

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I am grateful to Timothy C. Hain, MD, for permission to reproduce figure 1. From 'Brainstem strokes associated with vertigo or hearing symptoms' at <http://dizziness-and-balance.com/disorders/central/brainstem%20strokes.htm>.

² Organic osmolytes (idiogenic osmoles) accumulate intracellularly to protect cells from osmotic injury. Experimentally, amino acids such as taurine, glutamate, and glutamine accumulate in the brain of experimental animals with chronic hypernatremia. Myoinositol, glycerophosphorylcholine, and phosphocreatine/creatine are also organic osmolytes, which can account for the observed increase in brain osmolality during hypernatremic states.

References

- 1 Adams RD, Victor M, Mancall EL: Central pontine myelinolysis: a hitherto undescribed disease occurring in alcoholic and malnourished patients. *Arch Neurol Psychiatry* 1959; 81:154–172.
- 2 Adams RD, Victor M: *Principles of Neurology*, ed 5. New York, McGraw-Hill, 1993, pp 891–892.
- 3 Wright DG, Laureno R, Victor M: Pontine and extrapontine myelinolysis. *Brain* 1979; 102:361–385.
- 4 Thompson PD, Miller D, Gledhill RF, Rossor MN: Magnetic resonance imaging in central pontine myelinolysis. *J Neurol Neurosurg Psychiatry* 1989;52:675–677.
- 5 Tomlinson BE, Pierides AM, Bradley WG: Central pontine myelinolysis. Two cases with associated electrolyte disturbance. *Q J Med* 1976;45:373–386.
- 6 Burcar PJ, Norenberg MD, Yarnell PR: Hyponatremia and central pontine myelinolysis. *Neurology* 1977;27:223–226.
- 7 Laureno R, Karp BI: Pontine and extrapontine myelinolysis following rapid correction of hyponatraemia. *Lancet* 1988;i:1439–1441.
- 8 Laureno R, Karp BI: Myelinolysis after correction of hyponatremia. *Ann Intern Med* 1997;126:57–62.
- 9 Laureno R: Pontine and extrapontine myelinolysis following rapid correction of experimental hyponatremia. *Trans Am Neurol Assoc* 1981;106:98–101.
- 10 Martin RJ: Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. *J Neurol Neurosurg Psychiatry* 2004;75(suppl 3):iii22–iii28.
- 11 Sugimoto T, Murata T, Omori M, Wada Y: Central pontine myelinolysis associated with hypokalaemia in anorexia nervosa. *J Neurol Neurosurg Psychiatry* 2003;74:353–355.
- 12 Illowsky BP, Laureno R: Encephalopathy and myelinolysis after rapid correction of hyponatremia. *Brain* 1987;110:855–867.
- 13 Takefujia S, Murasea T, Sugimuraa Y, Takagishia Y, Hayasakaa S, Oisob Y, Murataa Y: Role of microglia in the pathogenesis of osmotic-induced demyelination. *Exp Neurol* 2007;204:88–94.
- 14 DeLuca GC, Nagy ZS, Esiri MM, Davey P: Evidence for a role for apoptosis in central pontine myelinolysis. *Acta Neuropathol* 2002;103:590–598.
- 15 Videen JS, Michaelis T, Pinto P, Ross BD: Human cerebral osmolytes during chronic hyponatremia. A proton magnetic resonance spectroscopy study. *J Clin Invest* 1995;95: 788–793.
- 16 Nomoto N, Arasaki K, Tamaki M: Central pontine myelinolysis in chronic alcoholism demonstrated by magnetic resonance imaging and spectroscopy. *Eur Neurol* 2004;51: 179–180.
- 17 Menger H, Jörg J: Outcome of central pontine and extrapontine myelinolysis *J Neurol* 1999;246:700–705.
- 18 Kumar S, Fowler M, Gonzalez-Toledo E, Jaffe SL: Central pontine myelinolysis, an update. *Neurol Res* 2006;28:360–366.
- 19 Brown WD: Osmotic demyelinating disorders: central pontine and extrapontine myelinolysis. *Curr Opin Neurol* 2000;13:691–697.