

Central Pontine Myelinolysis

In a decade of service in Neuropathology at the Boston City Hospital and 27 years as Bullard Professor of Neuropathology and Chief of the Neurology Service at the Massachusetts General Hospital, I was afforded the opportunity to discover a number of neurological diseases and clarify neurological phenomena. The best known are: asterixis, intention myoclonus (Lance-Adams Syndrome), the primacy of brain embolism as the leading cause of stroke, the vanishing embolus allergic uremic, and myeloma polyneuritis, the details of the clinico-pathologic relationships of basilar artery occlusion, the histopathology of acute and subacute bacterial meningitis, the neurology of brain death, the clinical aspects of normal pressure hydrocephalus, congenital muscular dystrophy, the pathology of B12, pyridoxine and pantothenic acid deficiencies, hepatic encephalopathy, acquired subacute hepatocerebral degeneration, human Eck fistula (porto-caval shunt), haemosiderosis of meninges, histopathology of ammonia intoxication, pituitary apoplexy, the primary lesions of diphtheritic polyneuropathy, the complete anatomy of Wernicke-Korsakoff disease, thiamine deficiency and its relationship to Wernicke-Korsakoff disease, the thalamic basis of global amnesia, striato-nigral degeneration, and transient global amnesia. All were observed and reported for the first time with various collaborators in our department. Central pontine myelinolysis (CPM), about which I was asked to write, was one of these. The following notation describes its discovery and current status.

Maurice Victor, then a Fellow in the Neurological Unit of the Boston City Hospital, was at the time assisting me in a broad study of the neurological effects of alcoholism. He had been asked to examine a stalwart middle-aged man with delirium tremens. A few days later he asked me to accompany him on a second visit, occasioned by an abrupt worsening of the patient's condition. When we examined him in detail it was noted that he was apparently quadriplegic, unable to chew, swallow or speak but with retained tendon reflexes and Babinski signs. He could move his eyes and his pupils reacted to light. He seemed to respond slightly to painful stimuli over his body and face. We thought the clinical picture corresponded to what I had earlier described with W Watson as 'pseudo-coma' (and others later, as the 'locked-in' syndrome). We suspected occlusion of the basilar artery. No further tests were made.

The patient died of pneumonia a few days later and I had the opportunity to examine his brain. The basilar artery was patent and there was no evidence of atherosclerosis. Particularly wide open was the territory of the upper extension of the basilar and posterior cerebral arteries which probably ruled out brain embolism. Horizontal sections through the mid-pons showed the entire basis pontis to be relatively firm but granular and grayish in appearance. Only the myelin in the peripheral rim of the pons and the tegmentum (except possibly the medial lemniscus) was intact. The Research Fellows in my laboratory had called the lesion an infarct, despite the absence of vascular causation. But when sections stained for cells, myelin and axis cylinders became available, I observed the nerve cells and axis cylinders throughout the lesion were intact. Only the myelin sheaths were destroyed and myelin products were in the early stages of phagocytosis. Some of the oligodendrocytes had degenerated. There were no infiltrates of inflammatory cells and the blood vessels were patent. Clearly the lesion was not an infarct.

In order to distinguish the pathology of this lesion from other known forms of myelin destruction, I introduced the term central pontine myelinolysis, thinking it would denote both the nature of the lesion and its topography. The initial

report appeared under the names of Victor, Adams and Mancall in 1959.¹ During the next few years, once the disease had come to medical attention, other specimens of the same type began to appear in the medical literature. Both males and females, mostly adults, were affected. Alcoholics predominated. As to its overall frequency, Victor and Laureno at the Cleveland Municipal Hospital found 9 cases amongst 3,548 successive autopsies (0.25%). Karp and Laureno² at Emory University in Atlanta called attention to its frequent association with severe hyponatremia; and Laureno, collaborating with Victor,³ reproduced this lesion in dogs by inducing hyponatraemia and rapidly restoring sodium levels with intravenous 3% saline solution.

When reviewed in terms of its pathology, the pontine lesion could vary in size from a few millimeters to almost the entire basis pontis and part of the medial lemniscus. Rarely it extended to the lower part of the midbrain. The medulla was spared. In exceptional cases, lesions of similar type have been found outside the pons – in the thalamus, subthalamus, cerebellar or cerebral white matter and elsewhere. With respect to the extra-pontine cases, one may be tempted to draw an analogy to Marchiafava-Bignami disease. However, the latter clearly destroys axons as well as myelin with cavitation and atrophy of layer III of the frontal cortex.

The diagnosis has been facilitated by recognition of the circumstances with which it is most often conjoined i.e. severe hyponatraemia with alcoholism, renal failure, liver failure or any condition leading to hyponatraemia such as chronic cachexia, bacterial infections and neoplasms. In children, it complicates severe burns. T2 weighted MRI scans reveal the pontine lesions with fidelity. By this technique one can see small 2-3mm lesions that may be asymptomatic as well as larger symptomatic but non-fatal ones. A few of the latter with substantial MRI-visible pontine myelinolysis have recovered after 6-12 months. MRI also has exposed some of the extrapontine lesions which may be unaccompanied by CPM.

As regards other aetiologies, there is no evidence of multiple sclerosis, post-infectious encephalomyelitis, acute necrotizing encephalomyelitis, any form of Marchiafava-Bignami disease, or any one of the genetic-determined encephalopathies. Sporadic cases have been, seemingly by chance, associated with Wernicke disease and various forms of alcoholic encephalopathies (acute delirium tremens, acute auditory hallucinosis, chronic auditory hallucinosis) as described by the author and colleagues.⁴

Regarding the hyponatraemic associations of CPM in adults, more than half are chronic alcoholics who have developed critical levels of low serum sodium from salt wasting of inappropriate antidiuretic hormone (SIADH) secretion. If serum sodium falls rapidly below 120 meq/L the patients become drowsy, confused, stuporous and comatose. The sodium level may reach 100 meq/L. The real danger comes with the rapid correction of the hyponatraemia by intravenous NaCl, at which time CPM develops. When the level of serum sodium is slowly restored (<10meq/24 hours), CPM does not develop. However, the rapid correction of serum sodium as the only factor in causation has been questioned by McKee and colleagues who demonstrated typical lesions postmortem in 10 of 139 severely burned children who had been subjected to severe hyperosmolality some days before death but not in the terminal phase.⁵ They were never hyponatraemic. Some factor other than hypoosmolality must be operative, perhaps a rapid change in electrolyte environment of the myelin sheaths in certain regions of the brain. Thus aetiology still needs further study. Nevertheless, we now know of at least one means of prevention.



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References

- Adams RA, Victor M, Mancall LE. *Central Pontine Myelinolysis*. Archives of Neurology and Psychiatry, 1959;91:154-72.
- Karp BI, Laureno R. *Pontine and extrapontine myelinolysis: a neurologic disorder followed by rapid correction of hyponatremia*. Medicine, 1993;72:359.
- Laureno R. *Central Pontine myelinolysis following rapid correction of hyponatremia*. Annals of Neurology, 1983;13:232-42.
- Victor M, Hope J. *The phenomenon of auditory hallucinations in chronic alcoholism*. J Nerv Ment Dis, 1958;126:451.
- McKee AC, Winkelman MD, Banker BQ. *Central pontine myelinolysis in severely burned patients: Relationship to serum hyperosmolality*. Neurology, 1988; 38:1211.