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Central Pontine Myelinolysis: A Complication of Hyponatremia or of Therapeutic Intervention?

REFERENCE: Haibach, H., Ansbacher, L. E., and Dix, J. D., **"Central Pontine Myelinolysis: A Complication of Hyponatremia or of Therapeutic Intervention?,"** *Journal of Forensic Sciences*, JFSCA, Vol. 32, No. 2, March 1987, pp. 444-451.

ABSTRACT: We report four cases of central pontine myelinolysis (CPM) that illustrate important features of the disorder. The condition is described mainly in the neurological literature and, to our knowledge, is not discussed in the forensic science journals. This disorder must be recognized and understood by the forensic science expert who addresses issues of liability. In cases of multiple motor deficits and death with a history of hyponatremia, CPM must be included in the differential diagnosis. Careful examination of the pons and adjoining structures must be performed. Myelin stains are advisable. The association of CPM with major illnesses, hyponatremia and the correction of hyponatremia by intravenous saline infusions is discussed.

KEYWORDS: pathology and biology, central pontine myelinolysis, hyponatremia, alcoholism, malnutrition, hypernatremia, saline infusion

In 1959, Adams et al. [*1*] described four cases with a unique demyelinating lesion in the base of the pons and a striking symmetric distribution that has become known as central pontine myelinolysis (CPM). Nearly 200 cases have been recorded since, largely in the neurological, neuropathological, and internal medicine literature. Several excellent reviews have been published [*2-5*], emphasizing different aspects. In particular, the association of CPM with hyponatremia or the rapid correction of hyponatremia with intravenous administration of sodium chloride-containing solutions has been much debated [*3,6,7*]. To our knowledge, no reports of CPM have appeared in the forensic science literature. The disorder is of interest to forensic science experts because they are expected to recognize the disorder and understand that CPM is commonly associated with major illnesses and that it might or might not be precipitated by therapeutic intervention.

We report four cases of CPM that have come to our attention in the last four years which illustrate important features of this disorder. Only two cases were diagnosed *antemortem*.

Received for publication 7 April 1986; revised manuscript received 16 May 1986; accepted for publication 19 May 1986.

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Case Reports

Case 1

The patient, a 53-year-old man with a past medical history of diabetes mellitus, hypertension, and myocardial infarction, was transferred from a local hospital with a recent history of low grade fever, muscle pain, and confusion progressing to coma. He died 17 days later at the Harry S. Truman VA Hospital (HSTVAH). His course was characterized by pneumonia, pulmonary failure, renal failure, and sepsis. Computed axial tomography (CT) of the brain and cerebrospinal fluid cultures were unrevealing. Treatment was supportive and included an antiviral agent and a broad spectrum cephalosporin for suspected encephalomyelitis. Notable among the serum chemistries at the time of transfer were hypokalemia, hypochloremia, and severe hyponatremia of 102 mmol/L, which was corrected with isotonic and hypertonic saline, as shown in Fig. 1. These abnormalities were attributed to diuretics and free water intake. The patient's mental status did not improve with the correction of the serum electrolyte abnormalities.

Significant autopsy diagnoses were CPM, acute and chronic ischemic changes in the watershed cerebral cortex, cerebellar ischemic changes, organizing pneumonia, arteriosclerotic and hypertensive cardiovascular disease, recent myocardial infarction with left ventricular failure and dilatation, and chronic relapsing pancreatitis.

Case 2

The patient, a 35-year-old woman with paranoid schizophrenia, was transferred from a local psychiatric hospital to the University of Missouri-Columbia Hospital and Clinics (UMCHC) for confusion, hyponatremia (102 mmol/L), hypokalemia, and hypochloremia secondary to self-induced vomiting and subsequent water drinking. The hyponatremia was corrected, as shown in Fig. 1, with intravenous infusion of isotonic saline. Her mental status improved promptly and she was discharged 2 days later to the referring institution with instructions to continue restriction of oral fluids. She was referred back 8 days later arousable

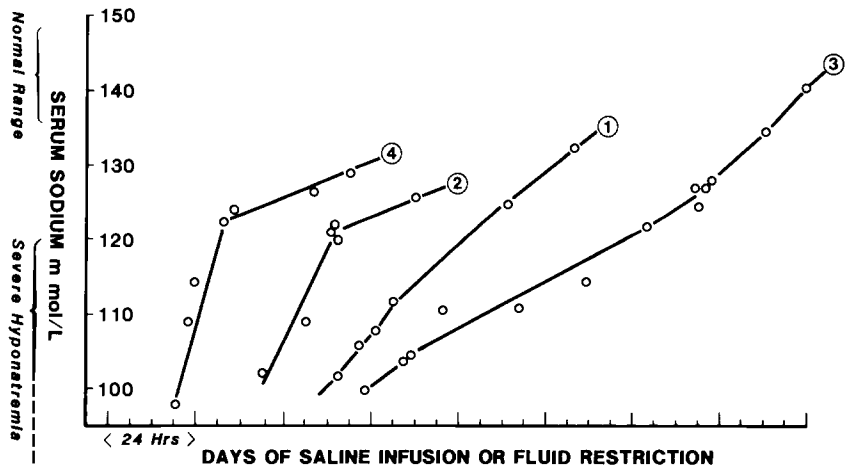

FIG. 1—*Correction of the serum sodium concentrations of Cases 1 through 4. Note the substantially slower rates of increase in Cases 2 and 4 after mild hyponatremic levels were achieved. The abscissa shows 24-h days with 6-h subdivisions during which saline was infused or fluid intake was restricted. Each case is started at a different point on the abscissa to avoid overlap of the curves.*

to mild physical stimuli, but not to verbal stimuli. There were spontaneous movements of her arms and legs. Electroencephalography revealed evidence of metabolic encephalopathy and mesencephalic conduction defects on auditory evoked response testing. CT with contrast enhancement, specifically searching for pontine lesions, was repeatedly unrevealing. The course in hospital was further characterized by continued coma, urinary tract infection, and sepsis with blood cultures positive for *Staphylococcus aureus*. The patient became afebrile after a course of antibiotics. Psychiatric and neurologic evaluations noted quadriparesis and possible mutism. The patient expired at the referring hospital 1 month later.

The medical examiner was notified and declined to take jurisdiction. The autopsy, performed by another pathologist, confirmed the clinical diagnosis of CPM. The lesion involved most of the basis pontis, but tapered at the upper and lower ends of the pons, and extended into the cerebral peduncles. There were no other significant findings.

Case 3

The patient, a 61-year-old man, was admitted to a local hospital with a history of weakness, chills, and leg pain of 2 weeks' duration. He was a chronic alcoholic. Fluid restriction was instituted because of a serum sodium concentration of 110 mmol/L. Intravenous infusion of hypertonic saline was begun when the sodium decreased to 100, and seizures occurred. Recovery of the serum sodium is shown in Fig. 1. The course in hospital was characterized by pulmonary edema, pneumonia, renal failure, hypotension, and continued stupor. Rectal bleeding developed, and his coagulation studies became abnormal. He was eventually transferred to the HSTVAH, where his course was complicated by deepening coma, congestive heart failure, thrombocytopenia, and anemia. CPM was suspected, and the diagnosis was supported by brainstem auditory evoked response testing. Persistent temperature elevation was considered to be of central origin. He died of respiratory arrest.

The autopsy confirmed the clinical diagnosis of CPM. On gross examination, the pontine lesion was subtle and nearly missed. Only edematous blurring of the normally sharp delineation of gray and white matter in the pontine base was evident. Other significant findings were hypertensive and arteriosclerotic cardiovascular disease with cerebral, splenic and renal infarctions, bilateral acute bronchopneumonia, ischemic colitis, peritonitis, and periportal fibrosis of the liver.

Case 4

The patient, a 61-year-old woman with a long history of hypertension, chronic obstructive pulmonary disease, and alcohol abuse, was admitted to UMCHC with recent profound weakness, vomiting, and diarrhea. She was confused and unable to stand without help. There was marked hyponatremia of 98 mmol/L, hypokalemia, hypochloremia, and alkalosis. Isotonic saline was infused and the hyponatremia corrected, as shown in Fig. 1. She became alert, oriented, and able to sit up. On the fifth day in the hospital, she lost bowel and bladder control. CT of the brain, electroencephalography (EEG), and lumbar puncture were unrevealing. On the sixth day, she became confused and developed slow speech and spasticity of both arms. Serum electrolytes were normal. On the tenth day, she opened her eyes in response when her name was called, but she could not speak or follow simple commands. The EEG showed temporal slowing. A brain scintigram as well as numerous tests for metabolic and toxic abnormalities were noncontributory. By the fourteenth day, there was no response to pain. Sputum cultures were positive for *Pseudomonas aeruginosa*. Temperature elevations reverted to normal after a course of antibiotics. Deep coma continued and she expired on the 29th day in hospital.

The autopsy revealed CPM with an approximately 2-by-2-by-2-cm demyelinating lesion in the caudal third of the pons which extended almost to the tegmentum. Other important

findings were acute myocardial infarction, bilateral bronchopneumonia, hepatosteatosis, chronic pancreatitis, and arterial and arteriolar nephrosclerosis.

Discussion

The cases described above serve to illustrate important features of CPM with regard to topography, clinical presentation, etiology, and forensic science implications.

The topography of the lesion is fairly constant [*1,2,8*]. In all four of our cases, there was symmetric involvement of the base of the pons, sparing the tegmentum, as shown in Fig. 2. In one case, the lesion extended into an adjoining structure, the cerebral peduncles. In general [*2,8,9*], at autopsy, serial cross sections of the pons reveal a well demarcated, slightly depressed, soft, gray-tan area in the base of the pons. The lesion assumes a diamond shape with the greatest extent present in the midpons. It tapers like a double pyramid to a point in

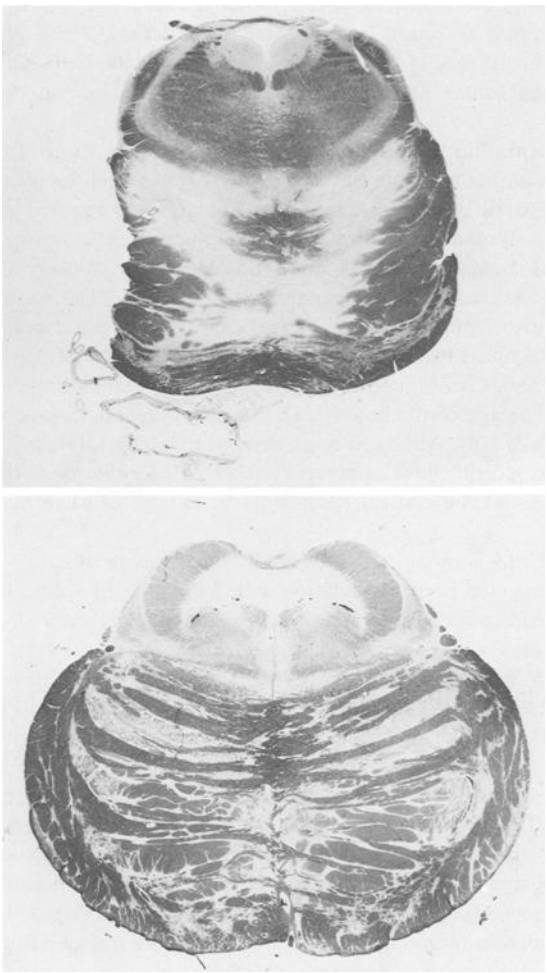

FIG. 2—*Cross sections of the pons, luxol fast blue stains, magnified* × *2.2.* Upper panel *Case 2, note symmetric demyelination affecting most of the section sparing the venterolateral tracts and the tegmentum.* Lower panel, *normal pons for comparison.*

the upper pons and at the pontomedullary junction. Larger pontine lesions extend into the cerebral peduncles or the medulla. The pattern betrays no predilection for tracts of certain origins or destinations, except that the ventrolaterally located corticospinal tracts are often spared [2,4]. Many associated extrapontine lesions with demyelination have been described [2,10]; however, questions have been raised whether these lesions share the same etiology or are ischemic in nature [3,10]. The variability of the neurological deficits elicited on clinical examination suggest a less constant topography in the nonfatal cases, as discussed below.

Although usually well-defined, the lesion can be very subtle on gross examination with only edematous blurring of the normally sharp definition of gray and white matter in the pontine base, as was noted in Case 3. This appearance may be related to the age of the lesion. The lesion can easily be missed, if not carefully searched for. Myelin stains have proved very helpful in demonstrating and clearly defining its extent.

Microscopically, there is usually total loss of the myelin sheaths and oligodendrocytes in the center of the lesion [1,2], a finding shared by our cases. The number of lipid-laden macrophages and reactive astrocytes increase with advancing age of the lesion. Vascular and inflammatory changes are characteristically absent, except for slight perivenular lymphocytic cuffing which may be found in the center of the lesion. Although most investigators [1,2] describe sparing of axons, all of our cases displayed axon balls indicating some degree of neuronal or axonal injury. Otherwise, the lesions of our cases matched the published descriptions.

The clinical presentation and outcome of CPM vary [11,12]. Confusion or stupor are part of the presentation and complicate the recognition of other neurological deficits, which include flaccid and spastic quadriparesis or quadriplegia accompanied in many instances by bulbar signs such as dysphagia and dysarthria. Hemiparesis, spastic weakness of both arms, and occulomotor abnormalities are recorded in milder cases. Sensory abnormalities do not develop, reflecting the sparing of the tegmentum pontis. The "locked-in" syndrome may be difficult to distinguish from confusion; both occur in CPM. Electroencephalography with brainstem evoked response testing and high resolution CT are helpful in confirming the clinical impression [13,14]. CT of the brainstem is technically demanding, and nonvisualization may be related to the age of the lesion [15]. Nuclear magnetic resonance (NMR) has also been used successfully [16]. Although most cases of CPM are fatal, survivals without major neurological defects recently have been reported [17,18]. Resolution of the CT abnormalities may lag months behind the clinical recovery [17]. Lately, CPM in children has been described [11,19].

The etiology of CPM is much debated [2-7]. Numerous predisposing factors have been described. Most discussed is the association with hyponatremia [2,5,7]. Severe hyponatremia was documented in our cases, as shown in Fig. 1, and a history of alcoholism was elicited in Cases 3 and 4. Case 2 was a compulsive water drinker. All of our cases have major chronic illnesses in common. Adams et al. [1], reporting the first cases of CPM, considered chronic alcohol abuse a cause. Malnutrition was soon added, yet there are many cases without either association [4,5]. Because the symmetry of the lesion resembles so closely the symmetric pattern of thiamine deficiency lesions, a deficiency syndrome has also been postulated for CPM [2]. Among other factors, excess antidiuretic hormone (ADH) [5,20], hypoglycemia, pH changes, renal failure, liver failure, lymphoma, and carcinomatosis have been implicated [5]. Studies by Barcar et al. [5] and Ayus et al. [3] support hyponatremia as a precipitating and predisposing factor. Laureno [6], citing largely animal studies [21-25], linked CPM to the rapid correction of hyponatremia. Norenberg and Papendick [15] believe that the chronicity of hyponatremia is an important factor. Since not all patients with hyponatremia develop CPM, and hyponatremia is not present in all patients with CPM [2], it must be emphasized that the association of CPM with hyponatremia remains tentative. There is, perhaps, less support for an association between CPM and rapid correction of hyponatremia, considering the very small number of patients studied. If one were to accept hyponatre-

mia as the cause of CPM, the intriguing question remains as to why the pons is more susceptible to the effects of hyponatremia than other brain tissue. According to the grid theory put forward by Messert et al. [4], the interlacing network of longitudinal and transverse fibers which is unique to the pons renders the tissue less distensible and thus more vulnerable to cerebral edema.

Severe hyponatremia itself requires prompt medical intervention, since it is a life-threatening abnormality causing decreased consciousness and predisposition to seizures [3]. Serum sodium concentrations of 98, 100, 102, and 103 mmol/L were documented in our cases and corrected with intravenous infusion of sodium chloride-containing solutions. As shown in Fig. 1, the initial recovery rate of our cases was 1.70, 1.00, 0.50, and 0.29 mmol/L/h up to the concentration of 125 mmol/L. In Cases 2 and 4, the increase was deliberately decelerated when this concentration was reached.

There is much debate whether rapid or slow correction of the hyponatremia with intravenous infusion of saline is the better therapeutic approach. The definition of "rapid" or "slow" varies depending on the investigator [3]. Rapid correction has ranged from 36 h to eleven days. Ayus et al. [3] tabulated data from the literature and their own laboratory and concluded that rapid correction of severe (< 120 mmol/L) to mild (mean 130 mmol/L) hyponatremia at a rate of more than 2,0 mmol/L/h is associated with a survival of 90%, as compared with a slow correction rate of approximately 0.6 mmol/L/h and 60% survival. Thus, severe hyponatremia requires prompt but only partial correction. In a few cases for which an association of CPM and rapid correction of hyponatremia was claimed, the serum concentration was raised to hypernatremic levels between 147 and 160 mmol/L [3]. Although there appears to be good reason to correct promptly severe hyponatremia, no need was demonstrated to correct to normal concentrations. Conversely, correction to normal or hypernatremia may be harmful [3]. Therefore, partial rapid correction of severe hyponatremia in a patient who subsequently develops CPM clearly is not to be viewed as a therapeutic misadventure. Available data are also insufficient to link firmly CPM to correction to normal or hypernatremic levels.

The medical literature contains no discussions of CPM specifically oriented toward the interests of the forensic science expert. The absence of publications on CPM in the forensic science journals may be explained by the fact that its association with hyponatremia has been described relatively recently. Cases of CPM, however, will come to the attention of the forensic pathologist with increasing frequency, as this awareness spreads throughout the medical profession. Given the high incidence of hyponatremia in major illnesses, it is justified to assume that CPM is underdiagnosed. Recognition of the clinical setting of CPM and its association with hyponatremia, infusion of iso- or hyper-tonic saline, alcoholism, and the pattern of neurological deficits should alert the prosector to include CPM in his differential diagnosis and to perform a careful examination of the pons and the adjoining structures, probably including myelin stains. Heavy metal poisoning [26] must also be excluded by specific toxological studies. The forensic pathologist may find it advisable to exclude this diagnosis by specific tests [27]. Furthermore, patency of the basilar artery and its branches must be ascertained.

As noted in the history of Case 2, the medical examiner (co-author J. D. D.) was notified but declined to take jurisdiction. A review of the case and its autopsy findings suggest he should have taken jurisdiction because there were questions concerning the propriety of the patient's medical management. Fortunately, permission for autopsy was granted and the question of possible therapeutic misadventure could be addressed. This case illustrates the need for better understanding of the etiology, clinical presentation, and autopsy findings of CPM by forensic science experts.

In a particular case, the medical examiner may be asked whether the therapeutic intervention by saline infusion to correct the hyponatremia caused CPM and resulted in permanent brain damage or death. This issue must be approached with caution and with sensitivity to

the complex clinical situation. Usually the patient has a serious illness or illnesses. Severe hyponatremia itself is a medical emergency requiring immediate attention because death can be sudden. Among those patients who are treated and survive, only a few may develop CPM. Rapid correction to mild hyponatremia has been associated with better overall survival rates than slower correction [*3*]. Considerations at the bedside give precedence to the immediate threat of hyponatremia over later occurring uncommon complications.

In summary, the review of the literature suggests several possible causes of CPM. The association with hyponatremia, although studied the most, remains tentative. Available data are also insufficient to link any of the therapeutic approaches for hyponatremia firmly to CPM, and the currently available data clearly are inadequate to support arguments in favor of settlements in litigation of alleged malpractice. Although there is evidence to discourage rapid correction to hypernatremia or normal sodium levels, the few cases in which there is an association with CPM cannot serve as a basis for claims of malpractice. As long as there may be multiple factors involved in the development of CPM, working either singly or in concert, no firm causal relation between CPM and any form of medical management of hyponatremia can be claimed. Substantially more data are needed.

Acknowledgments

The authors wish to thank Prudence Emery, HT(ASCP), for technical assistance and Betty Payne for help with the preparation of the manuscript.

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