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UPDATES

Myelinolysis after Correction of Hyponatremia

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Myelinolysis is a neurologic disorder that can occur after rapid correction of hyponatremia. Initially named "central pontine myelinolysis," this disease is now known to also affect extrapontine brain areas. Manifestations of myelinolysis usually evolve several days after correction of hyponatremia. Typical features are disorders of upper motor neurons, spastic quadriparesis and pseudobulbar palsy, and mental disorders ranging from mild confusion to coma. Death may occur. The motor and localizing signs of myelinolysis differ from the generalized encephalopathy that is caused by untreated hyponatremia.

Experiments have duplicated the clinical and pathologic features of myelinolysis by rapidly reversing hyponat remia in animals. Myelinolysis is more likely to occur after the treatment of chronic rather than acute hyponatremia and is more likely to occur with a rapid rate of correction. The exact pathogenesis of myelinolysis has not been determined.

Optimal management of hyponatremic patients involves weighing the risk for illness and death from untreated hyponatremia against the risk for myelinolysis due to correction of hyponatremia. Experiments in animals and clinical experience suggest that correction of chronic hyponatremia should be kept at a rate less than 10 mmol/L in any 24-hour period.

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Rapid correction of hyponatremia can cause a brain disease known as myelinolysis. This worldwide, iatrogenic problem has been documented in medical, surgical, pediatric, psychiatric, and obstetric settings. Although the disease was unknown 50 years ago, a clinical diagnosis of myelinolysis can now be made with confidence. More important, this disease can often be prevented by cautious treatment of hyponatremia.

Case Report

A 66-year-old woman was found convulsing on the floor 2 weeks after beginning therapy with diuretic medication. Her serum sodium concentration was 95 mmol/L when it was measured in the emergency department. Five hundred milliliters of 3% saline

was infused intravenously. On the second hospital day, the patient's serum sodium level had increased to 111 mmol/L, and she was awake and able to follow commands. Her serum sodium concentration increased further to 122 mmol/L by the next day, when an additional 800 mL of 3% saline was infused. The patient's condition continued to improve, and, after 4 days of hospitalization, her serum sodium concentration was 146 mmol/L. She was awake and alert and no longer required mechanical ventilation.

The patient had a seizure at 8 a.m. on the fifth day of hospitalization. Her serum sodium concentration at the time of the seizure was 139 mmol/L. After the seizure, she remained comatose. A magnetic resonance imaging (MRI) scan that was obtained 3 weeks after admission showed a symmetrical, hyperintense lesion in the center of the pons on T2-weighted images. This finding suggested central pontine myelinolysis (Figure 1). Bilateral thalamic and cerebral cortical lesions that were consistent with extrapontine myelinolysis were also evident. The patient's condition was further complicated by airway obstruction and hypoxia. She remained in a vegetative state until death. Figure 2 shows the central pontine lesion on autopsy.

History of Myelinolysis

The story of myelinolysis began in 1949 when a 38-year-old man with delirium tremens and pneumonia was admitted to Boston City Hospital in Boston, Massachusetts. Although he was strong on admission, he developed quadriplegia, facial weakness, dysphagia, mutism, and bilateral Babinski signs during hospitalization. The consulting neurologists, Maurice Victor and Raymond Adams, suspected a process in the basis pontis in which one lesion could affect both corticospinal tracts. Brain stem infarction seemed unlikely in this relatively young patient. On the one hand, the neurologic deficit was too extensive to be explained by occlusion of a penetrating branch of the basilar artery. On the other hand, the patient had no segmental brain stem signs, and the neurologic deficit was too limited to be explained by thrombosis of the basilar artery itself. The patient died after 22 days of hospitalization. Autopsy showed a lesion with striking bilateral symmetry in the center of the basis pontis. Microscopy showed that myelin was destroyed but that neurons and axons were relatively spared, a pattern of damage opposite that of infarction.

Ten years later, after evaluating three more cases with si milar lesions, Adams and colleagues (1) first described this condition as a clinicopathologic entity and named it "central pontine myelinolysis." They used the words "central pontine" to indicate the location of the lesion and the term "myelinolysis" to indicate that myelin was affected out of proportion to the neuronal elements (Figure 3, *left*). They specifically avoided the word "demyelination" to distinguish the pathology of myelinolysis from that of multiple sclerosis and related diseases in which inflammation accompanies myelin loss (Figure 3, *right*). Adams and colleagues emphasized the symmetry of central pontine myelinolysis and the invariant location of the disorder centered on the midline of the basis pontis. Neuropathologic disorders with symmetrical distribution that affect stereotyped locations in the brain are typically chemical in origin; therefore, Adams and colleagues deduced that the cause of myelinolysis was metabolic. They suspected a nutritional deficiency because all four of their patients were malnourished or alcoholic.

Hundreds of cases of central pontine myelinolysis have subsequently been described. In at least 10% of the reports, symmetrical areas of similar pathology were found outside the pons. These lesions have been called extrapontine myelinolysis (2).

In the mid-1970s, one of us encountered a patient with pontine and extrapontine myelinolysis at the Cleveland Metropolitan General Hospital in Cleveland, Ohio. She had initially presented with confusion and severe hyponatremia. Hypertonic saline therapy increased her sodium level from 109 mmol/L to 136 mmol/L during an 18-hour period. However, clinical improvement did not accompany the improved blood chemistry; in fact, the patient's condition deteriorated within days of treatment, and she became comatose and quadriplegic. The patient's neurologic illness was shown at autopsy to have been caused by central pontine myelinol ysis. In addition to the lesion in the pons, symmetrical extrapontine myelinolysis was found bilaterally in the thalamus, cerebellum, cortical and subcortical regions, and lateral geniculate body.

A survey of clinical reports on myelinolysis at that time showed that hyponatremia had been documented in many cases (3), especially those with extrapontine lesions (2). Our subsequent review of all pathologic cases of central pontine myelinolysis on file at Cleveland Metropolitan General Hospital showed a correlation between the histologic age of the lesion and the timing of the sodium abnormality, thereby strengthening the notion that the sodium disorder was not coincidental and supporting the suggestion of Tomlinson and workers (4) that rapid correction of hyponatremia rather than hyponatremia itself causes myelinolysis. We also found that in many of the patients most severely affected by myelinolysis (those with extrapontine and central pontine lesions), hyponatremia had been vigorously corrected. Later, Norenberg and colleagues (5) reported a correlation between the treatment of hyponatremia and the development of myelinolysis.

Experimental Data

On the basis of these clinical observations, we did experiments in animals to explore the relation between serum sodium and myelinolysis (6-8). Dogs were made hyponatremic by administration of vasopressin and intraperitoneal water. After several days of severe hyponatremia, the electrolyte imbalance was corrected by infusion of hypertonic saline and discontinuation of water and vasopressin administration.

The dogs, which were weak while hyponatremic, initially improved with treatment. Usually within 48 hours after normalization of the serum sodium concentration, however, the animals became paralyzed. At autopsy, myelinolysis was present symmetrically in the center of the pons, in thalmocapsular regions, and in subcortical white matter. Thus, the experimental model successfully duplicated the cli nical and pathologic features of human myelinolysis.

The experiments also showed a correlation between the rate of increase in serum sodium levels and the incidence of myelinolysis. When serum sodium levels increased faster than 14 mmol/L during the first 24 hours, 71% of the dogs showed lesions. Myelinolysis did not occur in animals whose serum sodium was increased more gradually, in animals with

uncorrected hyponatremia, or in normonatremic dogs that were infused with hypertonic saline.

Similar experiments in rats and rabbits duplicated and extended these findings (5, 9-15). To confirm that untreated hyponatremia alone did not produce myelinolysis, we induced and sustained severe symptomatic hyponatremia in rabbits (12). No animal surviving a week or more with severe, uncorrected hyponatremia had myelinolysis; this finding has also been confirmed in rats (16). In contrast, rabbits whose severe hyponatremia was rapidly corrected after only 3 days developed myelinolysis. Myelinolytic lesions were not seen when the duration of severe hyponatremia before correction was less than 24 hours.

The experimental animal models and retrospective analyses of cases in humans show that myelinolysis follows correction of hyponatremia but not untreated hyponatremia, that the risk for myelinolysis is greater with more rapid correction of hyponatremia, and that myelinolysis is more likely if hyponatremia is chronic (rather than acute) before correction.

Thus, as Adams and colleagues predicted from the neuropathology, myelinolysis clearly has a metabolic cause. Because serum sodium levels were not routinely measured in patients until the mid-1950s, data on serum sodium levels were not available in the early cases. Thus, the relation of myelinolysis to fluctuations in sodium levels could not have been recognized when the disease was first described.

Epidemiology and Clinical Aspects

Myelinolysis has been described around the world in young children and adults of all ages. In one series of 3500 autopsies of adults at an urban hospital (2), 1 of every 300 patients showed this lesion. Myelinolysis is especially common in patients who have had orthotopic liver transplantation, with a reported incidence of 13% to 29% at autopsy (17-21). Myelinolysis can follow correction of hyponatremia of any cause. Although alcoholism is often a factor, myelinolysis has been reported in relatively healthy persons with hyponatremia that was caused by gastroenteritis or diuretic therapy (as in the patient described in the case report).

Sterns and colleagues (22) reported neurologic complications in 25% of severely hyponatremic patients after correction of hyponatremia. Those authors confirmed the experimental finding that patients who had been hyponatremic for more than 48 hours before treatment were more likely to develop myelinolytic lesions than were those whose hyponatremia had been of shorter duration.

The initial symptoms of myelinolysis are usually mutism and dysarthria (23). Lethar gy and affective changes are also common and may be mistaken for psychiatric illness. The classic symptoms of myelinolysis (spastic quadriparesis and pseudobulbar palsy) reflect damage to the corticospinal and corticobulbar tracts in the basis pontis. These symptoms occur in more than 90% of patients (23). Additional symptoms occur if lesions extend to the midbrain, medulla oblongata, or pontine tegmentum. For example, lesions of the midbrain may cause pupillary and oculomotor abnormalities. Involvement of the pontine tegmentum may lead to a depressed level of consciousness and various cranial nerve signs. Extrapontine

myelinolysis may cause ataxia, irregular behavior, or such movement disorders as parkinsonism and dystonia (23-25).

The outcome of patients with myelinolysis varies: Some die, and others recover completely. Many patients improve gradually or only partially. In a review of 14 surviving patients, we found that bulbar dysfunction and spastic quad riparesis frequently persisted (23). Movement disorders, behavioral changes, and alterations in cognition sometimes emerged as late sequelae of myelinolysis, long after the initial treatment of hyponatremia.

The course of myelinolysis often appears biphasic. First, a generalized encephalopathy is caused by hyponatremia, which usually improves with elevation of the sodium level. Second, a neurologic syndrome caused by myelinolysis typically ensues 2 to 3 days after hyponatremia is corrected. The overt clinical course is not always biphasic, however. When the hyponatremic encephalopathy does not improve before myelinolytic symptoms emerge, there may be difficulty in recognizing that two separate disease processes are occurring sequentially (22, 23).

Myelinolysis was first described as a pathologic entity. However, a reliable diagnosis before death is now possible on the basis of the clinical syndrome and setting. Brain imaging is the most useful diagnostic test. Computed tomography (CT) shows centr al pontine and extrapontine lesions as symmetrical areas of hypodensity (26-28). Magnetic resonance imaging is more sensitive; lesions appear hyperintense on T2-weighted images (Figure 1) and hypointense on T1-weighted images (29-32). Myelinolytic lesions do not typically enhance with gadolinium. Because myelinolytic lesions may not be apparent on scans within the first 2 weeks of illness, later scans may be necessary to confirm the diagnosis (23). Thus, a diagnosis of myelinolysis should not be ruled out simply because brain imaging during the first 2 weeks of the illness does not show lesions.

Other diagnostic tests may be particularly helpful in distinguishing the syndrome of myelinolysis from the symptoms of hyponatremia. Examination of brain-stem auditory evoked potentials may show abnormally slow conduction through the brain stem (33, 34). The electroencephalogram shows slowing and may be of low voltage (23). Levels of cerebrospinal fluid protein and myelin basic protein may be elevated (23).

Medication aimed at alleviating such symptoms of myelinolysis as depression, psychosis, or parkinsonism may be effective, but myelinolysis itself cannot be specifically treated once symptoms have developed. Corticosteroids do not appear to be effective (23). Preliminary data from studies in animals suggest that relowering serum sodium in the initial hours and days after rapid correction may be beneficial (35, 36), but it is not yet known whether this strategy would be safe or effective in humans.

Untreated Hyponatremia

Hyponatremia causes generalized encephalopathy with manifestations that include malaise, nausea, headache, lethargy, confusion, seizures, coma, and death. Focal neurologic signs are rare. The severity of symptoms depends on the degree and rate of development of hyponatremia. A rapid decrease in sodium levels may lead to coma and seizures, but, if hyponatremia develops slowly, patients are much less symptomatic. Regardless of the rate of de cline, most patients have some symptoms if their serum sodium level is less than

125 mmol/L. Some studies suggest that young women sometimes have cardiorespiratory arrest caused by postoperative hyponatremia, but a major study at the Mayo Clinic (37) indicates that this rarely occurs.

Levels of cerebrospinal fluid protein and myelin basic protein are normal in hyponatremia but not in myelinolysis. In hyponatremia, the electroencephalogram is usually diffusely slow, and there may be triphasic waves that indicate metabolic encephalopathy. No focal brain lesions are seen on CT or MRI scans.

Uncorrected hyponatremia is not associated with myelinolysis (12). Verbalis and Martinez (15) maintained severe hyponatremia in rats for 22 days. The animals remained neurologically normal and did not show clinical signs or pathologic changes of myelinolysis.

Pathogenesis of Myelinolysis

Various studies (15, 38-42) have shown that the brain uses several mechanisms to avoi d severe edema during hyponatremia. Concentrations of sodium and potassium in the brain decrease within hours in the presence of hyponatremia. The brain also loses anions in the form of chloride and such organic osmolytes as phosphocreatine; *myo*-inositol; and the amino acids glutamine, taurine, and glutamic acid. With these adaptive measures, water content in the brain returns to normal within approximately 48 hours and remains stable thereafter (15, 16). Verbalis and Martinez (15) were able to sustain rats with profound hyponatremia for 3 weeks. At the end of that period, brain water content was normal; brain electrolytes and organic osmolyte levels were low but not significantly different than they had been 48 hours after the development of hyponatremia (15).

Once the brain adapts to hyponatremia, it is not well protected from the osmotic stress that accompanies correction of the condition (14, 43). Sodium and potassium content in the brain is restored during several hours, but organic osmoly tes take 5 to 7 days to return to normal levels. During rapid correction of chronic hyponatremia, the blood becomes hypertonic relative to the brain. In that circumstance, Sterns and colleagues (43) found cerebral dehydration that was avoided by more gradual treatment. However, Rojiani and colleagues (38) failed to confirm brain dehydration after correction of hyponatremia, although they did show intramyelinic edema, a breakdown of the blood-brain barrier, and oligodendrocyte degeneration as early pathologic abnormalities in myelinolysis. Mickel and colleagues (42) detected the oxidation of brain proteins with correction of hyponatremia.

Cerebral responses to hyponatremia and its correction offer clues to the mechanism of myelinolysis, but it is not yet known how these changes in brain osmolytes, hydration, blood-brain barrier competence, and oxidative stress relate to each other or how they cause myelin damage. The basis of the vulnerability of particular brain territories to myelinolysis is also uncle ar. Magnetic resonance spectroscopy may enable in vivo study of the brain's response to hyponatremia and its correction (44, 45).

Correction of Hyponatremia

Infusion of hypertonic saline has frequently been associated with myelinolysis because it quickly increases the sodium level. However, fluid restriction or isotonic saline infusion can also lead

to myelinolysis if the serum sodium level increases rapidly.

Myelinolysis can occur in settings other than rapid correction of hyponatremia. Soupart and colleagues (46) were able to induce myelinolysis by infusing mannitol into hyponatremic rats, thereby increasing osmotic pressure without correcting hyponatremia. In a different study (47), Soupart and colleagues reported myelinolysis in previously normonatremic rats with sustained, severe hypernatremia. Although human myelinolysis has been reported in the absence of documented hyponatremia, convincing evidence for a cause of myelinolysis other than serum sodium derangements is lacking.

Defining how rapid an increase in serum sodium concentration the brain can safely tolerate has been difficult. A retrospective series of cases in 1987 defined "too rapid" as faster than 25 mmol/L in 48 hours. Cluitmans and Meinders (48) (who reviewed the literature) and Sterns and colleagues (22, 49) (who reviewed their own cases) arrived at a similar figure of 12 mmol/L or more in 24 hours. This figure is close to the value of 14 mmol/L in 24 hours that was determined by the canine study discussed above (8). Verbalis and Martinez (15), reporting on studies in animals, considered both the rate and the magnitude of correction to be important. They found no myelinolysis in rats when the rate stayed less than 4 mmol/L h^{-1} and the overall magnitude stayed less than 25 mmol/L in 24 hours (15).

In our report of 14 cases of human myelinolysis after correction of hyponatremia (23), we found that in 21% of our patients, correction had been done in a fashion consistent with the so-called safe guidelines cited above. For example, one patient developed myelinolysis with a change in serum sodium concentration of 10 mmol/L at 24 hours and 21 mmol/L at 48 hours after the start of correction. One of the three patients in our series who developed myelinolysis despite correction of hyponatremia at so-called safe guidelines was alcoholic. However, none of these patients had more prolonged or severe hyponatremia or any other evident factor that might have predisposed them to myelinolysis despite a low rate of correction. Thus, although the data from clinical studies and studies in animals indicate a low incidence of myelinolysis if the increase in serum sodium is 12 mmol/L or less in 24 hours, it may be impossible to define a level of correction that is always completely free of risk.

Management of hyponatremic patients involves weighing the risk for illness and death from untreated hyponatremia against the risk for myelinolysis due to correction o f hyponatremia. The duration of hyponatremia and severity of symptoms should be considered. Regardless of whether hyponatremia is acute or chronic, saline infusion is usually not needed if patients are asymptomatic. Such patients can often be treated by removing factors that contribute to the hyponatremia. Discontinuing diuretic therapy, treating the underlying illness, or restricting fluids is adequate in many cases.

Even when hyponatremia is severe, moderation in therapy should be the rule. As long as the patient is clinically stable, the clinician should not be disturbed even by very low sodium levels: The patient, not the laboratory result, should receive treatment. If cerebral imaging shows no brain swelling or if the neurologic symptoms are mild, gentle correction should be the plan.

However, such severe symptoms of hyponatremia as repeated

convulsions, agitated confusion, or coma may require administration of saline. The sodium infusion should be stopped as soon as convulsions are co ntrolled and other symptoms begin to improve, regardless of the degree of persistent hyponatremia. Serum sodium levels must be closely monitored because they may increase with unexpected speed. If this occurs, relowering the serum sodium may be worthwhile. In any case, the rate of correction should be kept below 10 mmol/L during any 24-hour period, if possible.

Conclusion

Central pontine myelinolysis was first described as an idiopathic, clinicopathologic entity specifically, quadriplegia caused by a symmetrical central pontine lesion of characteristic histology. Subsequent observations have expanded our concept of the disease. We now know that symmetrical extrapontine lesions are frequently associated with the disorder. We have also learned that the clinical manifestations may be as mild as transient encephalopathy or may be absent altogether. Remarkably, in their early analysis of the disease, Adams and colleagues (1) correctly deduced from the symmetrical distribution and stereotypical location of central pontine myelinolysis that it has a metabolic cause.

Although articles appearing after the seminal paper suggested liver disease, renal disease, nutritional deficiency, and many other conditions as the metabolic cause, our data establish that the usual cause of central pontine myelinolysis is a rapid, sizable increment in the serum sodium level that usually occurs during correction of hyponatremia. Myelinolysis can occur regardless of the cause of hyponatremia or the specific method of its correction and can usually be avoided by cautious correction. Our data clearly indicate that correction of hyponatremia should be limited to less than 10 mmol/L within any 24-hour period whenever possible.

Future investigations will need to identify factors that may predispose a rare patient to myelinolysis after a small increase in serum sodium concentration. In addition, we hope to learn the precise mechanism by which a rapid increase in sodium concentration results in myelin injury.

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