what's your diagnosis?

Diagnosis: Osmotic myelinolysis (central pontine myelinolysis and extrapontine myelinolysis)

Asrar Ahmed, Rouf Asimi, Amit Sharma, Saima Nazir

From the Department of Neurology, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, India

Correspondence and reprint requests: Asrar Ahmed · her-I-Kashmir Institute of Medical Sciences · Soura-Neurology Soura · Srinagar Jammu and Kashmir, India · Srinagar Jammu and Kashmir 190011 · T: 9906598681 · asrar357@yahoo.co.in · Accepted for publication February 2007

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Osmotic myelinolysis (OM) is an acute, non-inflammatory demyelinating disease that can develop following rapid correction of hyponatremia from any cause. Adams and colleagues¹ originally described it in 1959, using the term central pontine myelinolysis, as a unique clinical entity affecting alcoholics and the malnourished. Since 1962, lesions outside the pons (extrapontine) were increasingly recognized, so the term "osmotic myelinolysis" seems to be more appropriate. In 1950, Adams and Victor observed a rapidly evolving quadriplegia and pseudobulbar palsy in a young alcoholic man whose postmortem examination disclosed a large, symmetrical, essentially demyelinating lesion occupying the greater part of the base of the pons. In 1959, Adams et al reported four more cases using the term central pontine myelinolysis.

The outstanding clinical characteristic of OM is invariably associated with other serious, often life threatening disease. In more than half the cases, it has appeared in the late stages of chronic alcoholism, often in association with Wernicke disease and polyneuropathy. Among other medical conditions and diseases with which OM has been conjoined are a malnourished status, chronic renal failure being treated with dialysis, diabetes mellitus, hepatic failure and post-orthotopic liver transplantation,² advanced lymphoma, carcinoma, severe bacterial infections, dehydration and electrolyte disturbances, acute hemorrhagic pancreatitis, and pellagra. It can also occur in healthy persons with hyponatremia caused by gastroenteritis or diuretic therapy. There are many reports of the disease in children, particularly in those with severe burns.³ Osmotic myelinolysis following treatment of hyponatremic dehydration is reported even during infancy.⁴ Young children and adults of all ages and both sexes can be affected. OM occurs sporadically, with no hint of a genetic factor.

The pathogenesis of myelinolysis, and the reasons for

vulnerability and predilection of particular brain territories to develop myelinolysis are not fully understood. Pathologically, the fundamental abnormality consists of destruction of the myelinated sheaths throughout the lesion, with relative sparing of the axons and intactness of the nerve cells. Signs of inflammation are conspicuously absent. In contrast this pattern of damage is opposite to that of infarction and the inflammatory demyelinations of multiple sclerosis and postinfectious encephalomyelitis. Classically, the central basis pontis is involved, hence the original name of central pontine myelinolysis (CPM). Very rarely, the lesion may encroach on the midbrain, but only very rarely does it extend down to the medulla. Exceptionally, the extensive pontine lesions may be associated with identical myelinolytic foci symmetrically distributed in the thalamus, subthalamic nucleus, striatum, internal capsule, corpus callosum, amygdaloid nuclei, lateral geniculate body, white matter of the cerebellar folia, and deep layers of the cerebral cortex and subjacent white matter. The latter condition is termed extrapontine myelinolysis (EM).

Clinical reviews and experimental animal models have shown that the main contributing factor for the development of myelinolysis is the correction of hyponatremia, first suggested by Tomlinson in 1976 and subsequently proved convincingly by Laureno in his work on dogs and by Kleinschmidt-DeMasters and Norenberg on rats.⁶ OM is especially likely to occur following rapid correction of hyponatremia (e.g., more than 12 mmol/L a day) and if the hyponatremia is chronic rather than acute prior to correction. Nevertheless, OM can still occur even after cautious and slow correction, especially in the presence of other recognized risk factors such as hypokalemia, liver or renal disease, and poor nutritional status. Hypokalemia, especially, has been reported as a possible trigger. About 90% of the cases reviewed by Lohr in 1994 were found to be hypokalemic⁷ (as was

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Figure 1a. Shows a trident-shaped area of T2 hyperintensity (arrow) in the central pontine region in the axial plane on cranial MR scan.

Figure 1b. Shows multiple areas of T2 hyperintensities in the basal ganglia and deep white matter (arrows), representing part of the same process as Figure 1a.

our patient). It is impossible to define a level of correction that will be absolutely free of risk. On the other hand, untreated hyponatremia, regardless of its severity, will not result in myelinolysis. In reference to the above, our patient had an initial serum sodium of 98 mEq/L

and serum potassium of 1.98 mEq/L at the time of presentation. Serum sodium and potassium were corrected over a period of time to normal levels but the patient developed progressive neurological deterioration. MRI of the brain later revealed typical features as described above.

The clinical course of affected patients may be biphasic. Following clinical improvement from hyponatremic encephalopathy, a neurologic syndrome caused by myelinolysis typically ensues 2-3 days after the correction of hyponatremia. Initial symptoms include mutism, dysarthria, lethargy and affective changes. Later, the classical symptoms of spastic quadriparesis and pseudobulbar palsy develop, reflecting damage to the corticospinal and corticobulbar tracts in the basis pontis. These symptoms may develop in more than 90% of patients. A large central pontine OM can cause a locked-in syndrome. Extrapontine involvement can present with varying movement disorders such as ataxia, dystonia and Parkinsonism.

Radiologically, OM manifests as regions of increased water content. Although CT scans of patients with clinically apparent CPM may show central pontine radiolucency, MRI is much more sensitive and the imaging method of choice for the diagnosis. The MRI discloses a characteristic "bat wing" lesion of the basis pontis in typical cases (Figure 1a and 1c). Lesions appear as hypointense in T1-weighted and hyperintense on T2-weighted acquisitions and are non-contrast enhancing. Enhancement following intravenous gadolinium-DTPA injection is rare though it has been reported. Imaging findings may not be apparent within the first 2 weeks of illness in some cases. For these reasons, a diagnosis of OM should not be ruled out simply on the basis of negative CT/MRI scans. There is also no correlation between the size of the lesions on imaging and the clinical severity of the neurological manifestations. The regions affected are also characteristic: CPM affects the basal pons with sparing of the descending corticospinal tracts as well as peripheral pontine tissue. The corticospinal tracts may appear as preserved islands within a zone of hyperintense pontine demyelination on T2-weighted MRI images. There may be a significant delay in the appearance of lesions on MRI and hence a repeat study after 2 weeks may be needed in cases where diagnosis is likely. EPM typically involves the basal ganglia and the lateral thalamic nuclei (Figure 1b). In a review necropsy series by Gocht and Colmant of 58 cases of OM, 27 cases had CPM, 18 had both CPM and EPM while 13 cases presented as isolated EPM.⁸

The signal intensity changes of OM on MRI are non-specific. Various other disease processes may some-

Figure 1c. Represents a midsagittal T2-weighted MRI image showing a triangular hyperintense lesion in the midpons (arrow).

what produce similar findings. Brainstem neoplasms such as glioma and metastasis may appear somewhat like OM, but usually present in a more subacute manner. Infarction, multiple sclerosis, encephalitis, and acute disseminated encephalomyelitis often show more diffuse involvement in the supratentorial regions, and therefore clinical differentiation is not problematic. Post-irradiation and post-chemotherapy changes can easily be diagnosed from the clinical history in most cases. Nevertheless, symmetrical involvement of the central pons on CT/MRI scans should suggest OM in the acute clinical setting, especially in the presence of recent sodium correction. Furthermore, concomitant involvement of the pons and basal ganglia is fairly specific of OM. Hypoxic encephalopathy, Leigh's disease and Wilson's disease are a few other differential considerations that can be excluded on clinical grounds.

Other diagnostic tests may be helpful in establishing the diagnosis of OM. Brainstem auditory evoked potential studies may identify pontine lesions early in the course of myelinolysis when imaging is normal. Routine CSF studies are usually normal, but CSF protein levels and myelin basic protein levels may be elevated in OM but not in hyponatremia. Electroencephalograms are non-specific and frequently show generalized slowing. Recently, 18-fluorodeoxyglucose positron emission tomography (PET) has been reported to show transient

glucose hypermetabolism in the pontine lesions in the early stage of the disease, which later evolved into a hypometabolic state.⁹

Treatment of myelinolysis is essentially supportive. Therapeutic guidelines for correction of hyponatremia are still being considered. Karp and Laureno, on the basis of their experience and that of Sterns et al, have suggested that the hyponatremia be corrected by no more than 10 mEq/L in the initial 24 hours and by no more than about 21 mEq/L in the initial 48 hours. Medications can alleviate symptoms of myelinolysis such as depression, psychosis and abnormal somatic movements. The myelinolysis itself cannot be specifically treated once it develops. Recently, therapeutic plasmapheresis has been reported as a safe and effective method of improving the clinical outcome. Although OM was once believed to be fatal with a survival rate of only 5% to 10% beyond 6 months, it is now clear that many patients survive much longer. The clinical outcome varies widely, and recovery can be complete or partial. Recommendations for management of hyponatremia stress the importance of slow correction; not more than 10 mEq/L in the initial 24 hours and by no more than about 21 mEq/L in the initial 48 hours.^{10,11} Once it develops, myelinolysis itself cannot be treated but symptoms of depression, psychosis and abnormal somatic movements can be alleviated with medication. The clinical outcome varies widely, and recovery can be complete or partial.

In conclusion, OM (CPM and EPM) is a distinct entity with a unique clinical presentation resulting from aggressive treatment of chronic severe hyponatremia, with a possible contribution from associated hypokalemia as well. Physicians should be aware of this entity when dealing with hyponatremic patients. Management involves weighing the risk of the illness and possible death from untreated hyponatremia against the risk of developing OM. Obviously the duration of hyponatremia and the severity of related symptoms should be taken into consideration. Although radiological findings of OM are not specific, MRI is the radiological modality of choice in investigating suspected OM, and it is usually, but not exclusively, positive, within 2 weeks of onset of symptoms. Resolution of MRI findings appears to follow clinical improvement but bears no constant relationship. Ultimately the clinical picture remains the best guide to the patient's prognosis. An individual prognosis is difficult due to varied clinical outcomes including death, disability or complete recovery.

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errata

Vol 27;1 (January/February 2007): On page 37, Figure 2 was labeled as an MRI scan. It should have been labeled as a CT scan of hydatid cysts in the right paravertebral region.

Vol 26;5 (September/October 2006): On page 398, one of the author's names was misspelled. The correct spelling is Hatem A. Khalaf, not Khalef.

Vol 20;1 (January 2000): On page 83, one of the author's names was misspelled. The correct spelling is Ahmed Bahammam, not Bahamman.