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CE - MEDICAL ILLUSTRATION

Osmotic demyelination syndrome: plasmapheresis versus intravenous immunoglobulin?

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A 63-year-old man with a past medical history of nonalcoholic steatohepatitis cirrhosis complicated by hepatic encephalopathy and non-bleeding esophageal varices presented for orthotopic liver transplantation. The patient had no acute complications in the immediate post-operative period, and was extubated on post-operative day (POD) 1. At that time, he was neurologically intact, alert and oriented and with no focal neurological deficits. On POD 3, he became lethargic and quadriplegic (Medical Research Council Scale Grade 0), and developed right-sided focal seizures with secondary generalization. His serum sodium was 128 mmol/L. He was re-intubated, and treated for his seizures with lorazepam 4 mg and levetiracetam 2 g, and then continued on levetiracetam 1 g two times a day. The following day, he was unresponsive and had no motor response to painful stimuli. His serum sodium had corrected without additional exogenous intervention to 135 mmol/L. On post symptom onset day (PSOD) 3, an MRI brain without contrast showed chronic small vessel ischemic changes but no other abnormality (Fig. 1a). The EEG did not show any seizure or epileptiform discharges. Serum chemistry and cerebrospinal fluid analysis did not show any significant abnormalities. On PSOD 13, his presentation remained the same. An MRI brain was repeated showing DWI restriction and high T2 signal in the central pons, suggestive of ODS (Fig. 1b). On PSOD 19, he was started on both IVIG and PP for a total of 5 days. Approximately 3 weeks after treatment with IVIG and Plasmapheresis, a repeat MRI showed similar prominence of T2 hyperintensity in the central pons with sparing of the periphery as compared to prior, findings consistent with central pontine myelinolysis/osmotic demyelination syndrome (Fig. 1c). Over the next 90 days the patient improved, becoming fully alert, regaining spontaneous muscle flicker in all four extremities (Medical Research Council Scale Grade 1), full eye movements and the ability to swallow.

Osmotic demyelination syndrome (ODS) is a disorder characterized by the destruction of neuronal myelin sheaths in either the central area of the pons as in central pontine myelinolysis (CPM), or in other susceptible areas such as the basal ganglia, hippocampi or cerebellum known as external pontine myelinolysis (EPM). CPM can present with T2 hyperintensities on MRI in a classic trident-shape pattern. ODS usually presents as a complication of rapid correction of hyponatremia. Although no specific treatment has been described, plasmapheresis (PP) and intravenous immunoglobulin (IVIG) have been suggested as possible options for the management of ODS [1]. A clear association has been established between rapid correction of hyponatremia and the development of ODS. Although not completely understood, the pathophysiology of ODS classically described is the reduced extracellular osmolality causing brain cells to release osmotically-active substances in an attempt to achieve osmotic equilibrium. These osmotic substances cannot be reabsorbed rapidly, and when sodium levels are increased, they create an osmotic stress that leads to a disruption in the blood brain barrier, leading to myelinolysis. In addition, the death of oligodendrocytes via apoptosis from osmotic shifts has also been suggested

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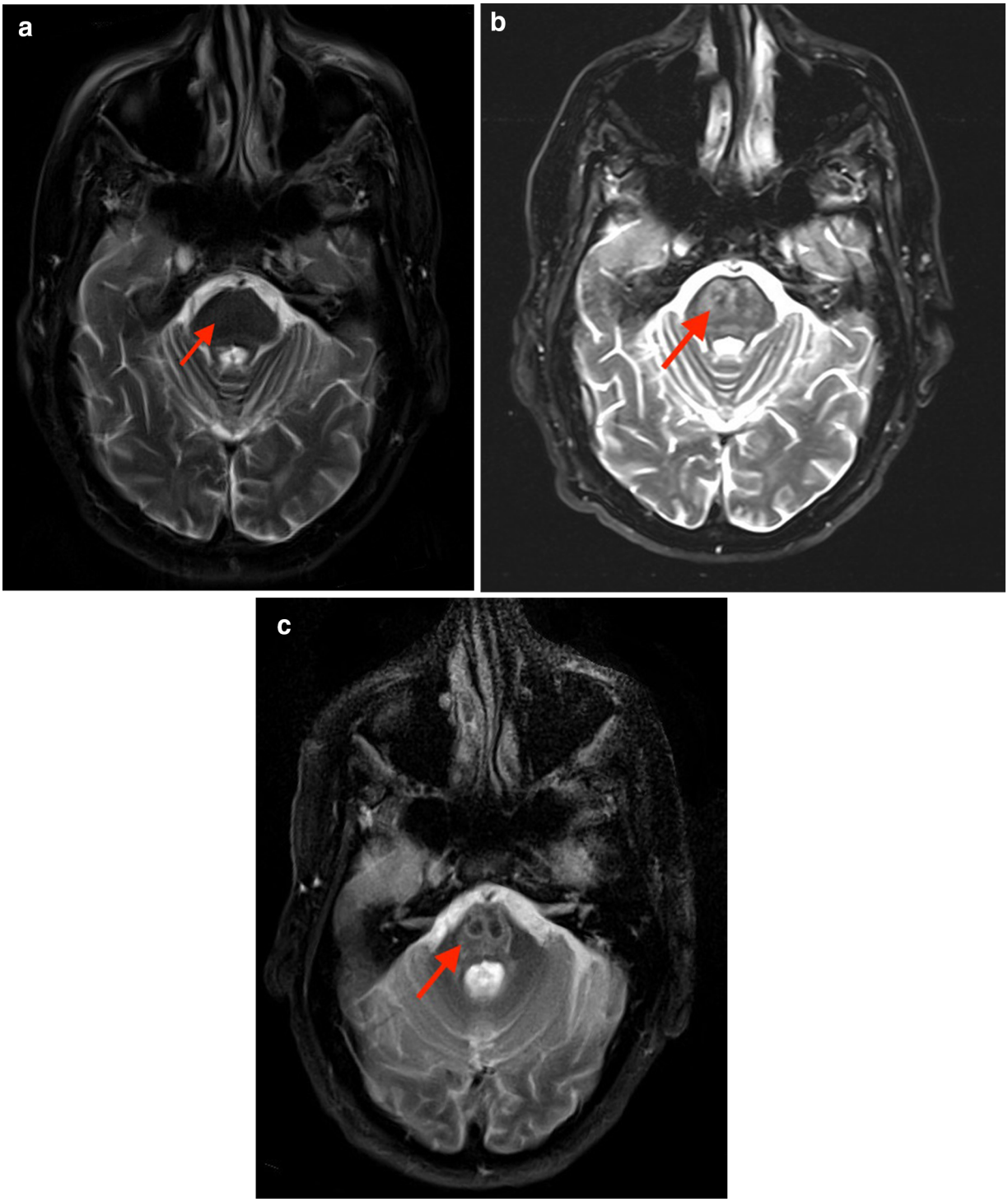

Fig. 1 **a** Post symptom onset day 3. *MRI* normal T2 appearance of the central pons without evidence of hyperintensity. **b** Post symptom onset day 13. *MRI* confluent T2 hyperintensity in the central pons findings consistent with central pontine myelinolysis/osmotic demyelination syndrome, possibly subacute. **c** Approximately 3 weeks after treatment with IVIG and plasmapheresis. *MRI* similar prominence of T2 hyperintensity in the central pons with sparing of the periphery as compared to prior, findings consistent with central pontine myelinolysis/osmotic demyelination syndrome

as an additional mechanism that contributes to the pathophysiological process. In our patient, the hyponatremia was corrected itself without additional exogenous intervention from 128 to 135 mmol/L within 24 h (on day 3). We suspect this resulted from rapid volume and electrolyte fluctuation due to liver transplantation. By the time the

Table 1 Summary of all reported osmotic demyelination syndrome (ODS) cases receiving IVIG or/and PP

References	Involvement	Comorbidity	HypoNa/ rapid correction	Treatment (Rx)	Rx initiation after confirm	Dosage	Outcome
Bibl et al. [1]	CPM	CAA	Yes/yes	PP	Immediately	24,700 mL	Complete motor recovery, minimal ataxia
	CPM	N/A	Yes/no	PP	Immediately	5243 mL	Walk with assistance
	CPM	CAA	Yes/no	PP	Immediately	18,270 mL	Complete motor recovery
Grimaldi et al. [6]	CPM	CAA	Yes/yes	PP	N/A	37,300 mL	Walk without assistance
Chang et al. [7]	CPM	Overdose of sodium bicarbonate	No/no	PP	N/A	4394 mL	Complete motor recovery, mild diplopia
Finsterer et al. [8]	CPM	CAA	Yes/no	IVIG	5 days	0.4 g/ kg/day × 5 days	Walk without assistance, mild dysarthria and ataxia
Deleu et al. [9]	CPM, EPM	N/A	Yes/yes	IVIG	7 days	0.4 g/ kg/day × 5 days	Improve in weakness and eat independently
Mastrangelo et al. [10]	CPM, EPM	Rapid correction of hypernatremia	No/no	IVIG	N/A	N/A	Near complete recovery
Murthy et al. [11]	EPM	N/A	Yes/yes	IVIG	1 day	5 days	Complete motor recovery
	EPM	Panhypopituitarism	No/no	IVIG	N/A	5 days	Complete motor recovery
	CPM, EPM	CAA	Yes/yes	IVIG	7 days	N/A	Moderate neurological recovery
Ludwig et al. [12]	CPM	Post liver transplant	Yes/no	PP, IVIG	2 days	PP 21,870 mL, IVIG 0.4 g/ kg/day × 5 days	Complete motor recovery
	CPM	Post liver transplant	Yes/no	PP, IVIG	2 days	PP 17,097 mL, IVIG 0.4 g/ kg/day × 5 days	Walk without assistance
Saner et al. [13]	CPM	Post liver transplant	No/no	PP, IVIG	N/A	PP 24,000 mL, IVIG 0.4 g/ kg/day × 5 days	Walk without assistance, mild dysarthria and ataxia

laboratory values had returned, the rapid correction had already occurred. A possible mechanism for hyponatremia correction in liver failure patients mentions heightened susceptibility to astrocyte metabolism resulting in abnormalities of blood–brain barrier function and a decreased ability to generate new intracellular osmoles in response to osmotic changes [2]. The mechanism of action in which PP and IVIG improve neurological outcome of ODS is unknown. One proposed theory is that myelinotoxic products are released after the osmotic stress insult and the burden maybe reduced by PP [1]. One other proposed theory is ODS may be a result of immunologic process, and thus IVIG treatment may help improve the outcome.

Radiologic studies in ODS can be negative during the first 4 weeks after the onset of clinical symptoms, and a negative imaging cannot exclude the presence of the disorder [3, 4]. Head CT typical findings are an area of hypodensity in the central pons, but this change is poorly sensitive [5]. The brain MRI is more reliable for diagnosing ODS. Typical findings for CPM are symmetric trident-shaped increase signals in the central pons on T2-weighted and FLAIR, and decreased signals in the T1-weighted images [3]. Diffusion weighted images can show a restricted diffusion pattern more rapidly, and can possibly be more useful for initial diagnosis. Being an uncommon condition, the standard of care consists mainly of supportive care to prevent complications including respiratory failure. An extensive literature search through PubMed for all reported cases of ODS receiving treatment of IVIG, PP, or both, with a total of nine articles were found and summarized (Table 1).

Drawing from available case reports, PP, IVIG, or the combination may provide treatment strategies for patients

with ODS. Remarkable improvement has been seen as soon as 1 day post treatment and complete recovery of neurological function established in some patients. In our case of ODS post liver transplantation who was treated with IVIG and immunoglobulin, our patient showed suboptimal improvement in motor weakness compared to other reported cases. In most of the reported ODS cases successfully treated with IVIG and PP together, or either alone, treatment was initiated within the first week of symptom onset and less than 5 days after confirmation by imaging studies (Table 1). However, our patient was started on treatment 19 days after symptoms onset because of the delay in diagnosis after the initial MRI imaging was negative. We hypothesize the delay in treatment initiation contributed to a worse outcome. The usual clinical presentation of ODS is often irreversible neurological symptoms, and we believe that this is due to a time-sensitive damage from the myelinotoxic compound that may be reversible if the offending agent is removed in time with the treatment of PP and IVIG.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent As with all case reports from my institution, waiver of informed consent was granted by the IRB.

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