Therapeutic Plasma Exchange as a Treatment for Central Pontine Myelinolysis in a 41-year-Old Male with Chronic Renal Insufficiency: A Case Report

Guillermo III Lacuesta Manalo, MD,[1,3] Aurelio Pantaleon S Reyes, MD,[2] Jane Wendolyn Wong Lu-Reyes, MD,[1] Catherine Matnao Carabbacan, MD,[1] Joice Bumanglag Dela Cruz, MD,[1] Marie Joyce Urnos Santos, MD,[1] Donaryn Villa Pasamonte, MD,[1] Sheryll Juan Pascual, MD,[1] and Deanna Dauz Quilala, MD[1]

Case Summary

Therapeutic plasma exchange (TPE) has been reported as a possible treatment for osmotic demyelination syndrome – central pontine myelinolysis (ODS-CPM), a degeneration of myelin within the central nervous system related to rapid hyponatremia correction, which though uncommon, has significant morbidity, and has no established specific treatment.

We present our experience with a 41-year-old male with chronic kidney disease, maintained on steroids, who presented with lethargy and behavioral changes. Initial metabolic panel showed severe hyponatremia (Na 109 mEq/L). Despite cautious sodium correction, the patient's sensorium decreased further and was intubated. Involuntary movements of the left face and arm were later seen. T2/FLAIR hyperintensities in the brainstem and thalami affirmed the diagnosis of ODS. A total of nine cycles (one cycle every two to three days) of TPE were completed. The patient was discharged with improved sensorium, from E2VxM4 to E4VxM6, and with no indication for hemodialysis due to improved creatinine. One year later, the patient has no remaining neurologic deficits.

Our experience supports other case reports that TPE is a viable therapy for ODS-CPM.

Key words: Therapeutic plasma exchange, Central pontine myelinolysis, Chronic renal insufficiency

Introduction

Central pontine myelinolysis (CPM) or osmotic demyelination syndrome (ODS) develops after rapid correction of hyponatremia, associated with demyelination of the pons. The disruption of the blood-brain barrier occurs secondary to osmotic stress and is thought to be one of the leading factors in the pathogenesis of CPM. It was estimated to have a prevalence rate of 1.72% in the United States general population, and an incidence rate of 0.611 per million person-years from 1997 to 2011 in Sweden.[1,2] Histopathologically, three cases were reported to have symmetrical lesions in the base of the pons and involving demyelination of all nerve tracts, appearing to originate from the center and spreading radially. These lesions were remarkable for the lack of oligodendrocytes and inflammation.[3] There are no specific diagnostic or treatment guidelines for ODS, but cases successfully treated with trials of re-lowering of sodium; levodopa, intravenous immunoglobulin, and dexamethasone; aggressive physical and speech therapy; and plasma exchange have been reported.[4-7] The clinical manifestations are irreversible or partially reversible, such as behavioral disturbances, involuntary movements, confusion and disorientation.[8-10] However, in our case, we were successful in reversing these manifestations with therapeutic plasma exchange (TPE); and we present our experience here.

Case Presentation

A 41-year-old male presented at the emergency room with behavioral changes.

He has had pre-existing hypertension and diabetes for five years, but these were reported to be well-controlled.

[1] Mariano Marcos Memorial Hospital and Medical Center, Barangay 6 San Julian, Batac City, Ilocos Norte
[2] Allied Care Experts Medical Center, Valenzuela City, Philippines
Corresponding author: Guillermo Lacuesta Manalo Email: terc81@yahoo.com

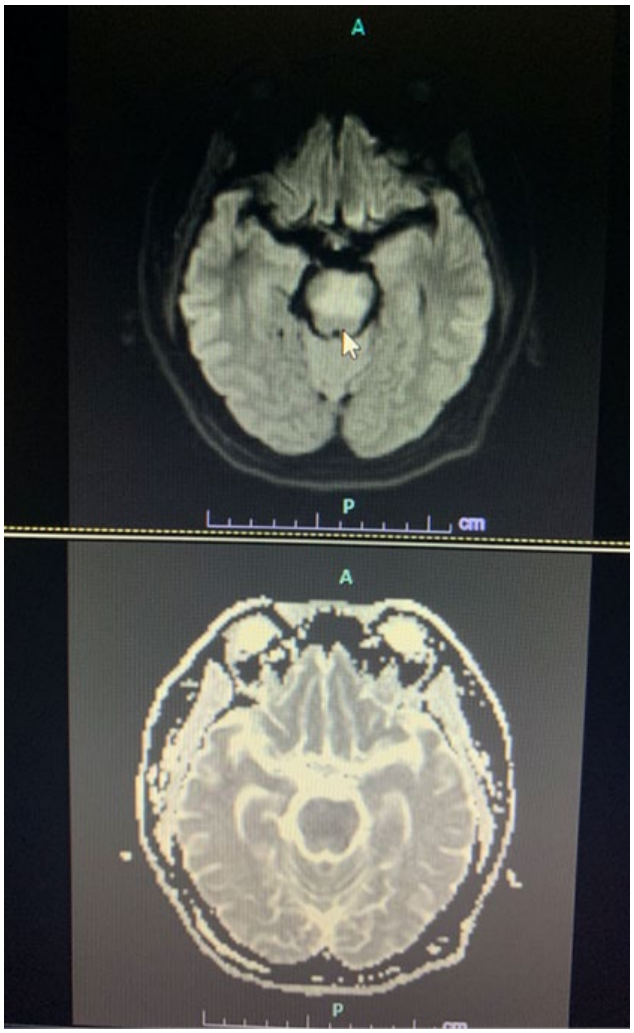

Fig. 1: Fluid-Attenuated Inversion Recovery (FLAIR, above) and T2 (below) cranial MRI images, showing a prominent pontine hyperintense lesion (white arrow).

Three months prior to admission, due to his persistently increasing creatinine, he was started on hemodialysis due to probable chronic kidney disease. Upon seeking second opinion, chronic glomerulonephritis was considered as his etiology of kidney disease, and, after a favorable trial of high-dose steroids which reduced his creatinine levels, hemodialysis was stopped. No renal biopsy was done to confirm the diagnosis.

Four days prior to admission, he presented with alternating episodes of restlessness and drowsiness, with disorientation and inappropriate responses to questions. These were also associated with poor oral intake. At this time, his steroid dose had been reduced to prednisone 15 mg/day.

There was no cough, fever, or urinary symptoms.

He had a strong family history of hypertension and heart disease.

Blood pressure on admission was 210/120, pulse rate was 115 beats per minute, respiratory rate was 24 cycles per minute. The patient was 165 cm tall, and weighed 95 kg. He was pale, with occasional crackles on auscultation. There was no lateralizing body weakness.

Initial laboratory tests showed severe hyponatremia (Na 109 mEq/L); thus, cautious sodium correction was done. He was transferred to a tertiary medical center for continuity of care. The doses of his oral and intravenous antihypertensives (clonidine, amlodipine, irbesartan, hydrochlorothiazide, nicardipine) were gradually increased for better blood pressure control. Despite these, the patient's symptoms progressed; he had fever and desaturations on the second hospital day, requiring intubation and mechanical ventilation. Midazolam 0.1 to 0.4 mg/kg was infused to address patient-ventilator asynchrony. Treatment for bacterial pneumonia with cefepime and azithromycin was started after COVID-19 was ruled out by reverse transcriptase polymerase chain reaction. Oral prednisone was shifted to intravenous hydrocortisone 40 mg every eight hours. Hemodialysis was initiated due to deteriorating kidney function.

Even with the lowering of his midazolam dose, he remained drowsy to stuporous, becoming E2V1M4 at best. Focal myoclonus of his left face and arm were also observed.

Differential diagnoses for his decreasing sensorium and focal myoclonus included viral or bacterial encephalitis, basilar artery infarction and uremic encephalopathy. Insulin was also started to control his increasing blood sugars. However, by the end of his first hospital week, cranial computed tomography scan and cerebrospinal fluid analysis were unremarkable. No cortical electroencephalographic correlation was found for his focal myoclonus. His antibiotics were later shifted to meropenem due to poor clinical improvement. He eventually underwent tracheostomy due to difficulty with weaning.

On the 17th hospital day, brain magnetic resonance imaging (MRI) was done due to the clinical suspicion of a centrally located lesion leading to the absence of his spontaneous breathing (*see Figure 1*).

There was a prominent pontine lesion exhibiting restricted diffusion on Diffusion-Weighted Imaging (DWI), hypointense on T1-weighted imaging, and with borders exhibiting hyperintense signals on T2-weighted imaging/FLAIR. Symmetrical bright signals were also noted on T2-weighted imaging/FLAIR at both thalami. The pontine and thalamic findings were consistent with osmotic demyelination syndrome. At this time, brainstem reflexes remained intact, but the best Glasgow Coma Scale (GCS) score was E2V1M4.

Although there are no well-studied therapies for ODS-CPM, a literature search by the family suggested that plasma exchange might be of benefit. Despite the low level of evidence, the patient's family consented to a treatment trial of therapeutic plasma exchange. The patient underwent nine sessions of therapeutic plasma

exchange from his 19th to 33rd hospital day (approximately one cycle every two days). The day following the first plasma exchange, patient's neurological symptoms improved; the involuntary movements ceased; and the patient started to spontaneously open his eyes and follow simple commands, improving to GCS E3V1M6. His creatinine levels also became normal, and hemodialysis was no longer indicated by the 5th cycle for TPE, until after he was discharged on his 44th hospital day.

At home, his general muscle strength was 1/5 to 2/5. At four months, he could already tolerate reclining at high back rest. His muscle strength improved to 3/5, and he was able to sit unassisted, at six months. He was able to stand unassisted by eight months. One year later, none of his neurologic complaints remained, and he was independent in all activities of daily living. Repeat cranial imaging was deferred by the family due to his marked clinical improvement. Due to the COVID-19 pandemic, however, decannulation of his tracheostomy has not yet been done, and he has not yet been able to return to work.

Case Discussion

Hyponatremia induces generalized cellular swelling, a consequence of water movement down the osmotic gradient from the hypotonic extracellular fluid (ECF) to the intracellular fluid (ICF). The symptoms of hyponatremia are primarily neurologic, reflecting the development of cerebral edema within a rigid skull. The initial CNS response to acute hyponatremia is an increase in interstitial pressure, leading to shunting of ECF and solutes from the interstitial space into the cerebrospinal fluid and then on into the systemic circulation. A key complication of acute hyponatremia is normocapnic or hypercapnic respiratory failure. The associated hypoxia may amplify the neurologic injury. Lesions of ODS classically affect the pons, a neuroanatomic structure wherein the delay in the reaccumulation of osmotic osmolytes is particularly pronounced. Patients with central pontine myelinolysis can present one or more days after overcorrection of hyponatremia with paraparesis or quadriparesis, dysphagia, dysarthria, diplopia, and loss of consciousness. Reaccumulation of organic osmolytes by brain cells is attenuated and delayed as osmolality increases after correction of hyponatremia, sometimes resulting in degenerative loss of oligodendrocytes and ODS.[11]

The patient also presented with focal myoclonic twitching of the left face and arm; electroencephalography was necessary to rule out *epilepsia partialis continua*. In the early days of the COVID-19 pandemic when this patient was admitted and COVID-19 testing was limited, viral encephalitis from COVID-19 was a valid consideration. It has since been reported that COVID-19 can indeed present with myoclonus.[12] Eventually, however, the patient's cerebrospinal fluid studies did not support a central nervous system infection, and SARS-CoV-2 mRNA was not detected by reverse transcription polymerase chain reaction (RT-PCR).

There are no specific diagnostic tests for osmotic demyelinating syndrome. History, physical examination, low serum sodium, a T1-hypointense, T2-hyperintense "batwing" lesion in the basis pontis, and similar lesions in the thalami and basal ganglia on cranial magnetic resonance imaging, often establish the diagnosis. Other tests include brainstem auditory evoked potentials and lumbar puncture, but these are non-specific.[13]

In the study of Bibl et.al, three patients were treated with plasma exchange for three to seven weeks (daily for four days, then twice weekly thereafter), and their neurological symptoms improved within two to twelve months.8 Because undefined myelin-toxic compounds released by osmotic stress are hypothesized to contribute to the irreversible demyelinating process in CPM, therapeutic plasma exchange may exert its effect by reducing these high-molecular weight myelin-toxic substances, leading to clinical improvement. This theory may explain why plasma exchange is effective in managing CPM due to acute hypernatremia. The most common adverse reactions of TPE are fever, chills, urticaria, muscle cramps, or paresthesias. These reactions were reported to be encountered more frequently when plasma was used as replacement fluid. In our case, we used albumin as replacement fluid so we did not encounter any adverse reaction. Metabolically, hypocalcemia is the most common electrolyte imbalance that may happen, so replacement is done with intravenous calcium gluconate.[14,15] Improvement of the nerve cells or neuron system is unlikely to occur with a single session of TPE.[1,16] In our case, plasma exchange was done every two days based on our co-author's clinical experience that hypocalcemia risk is less than if the procedure was done daily.

Summary

In the presented case, the introduction of TPE in the chronic phase of ODS-CPM improved the patient's neurological symptoms. This treatment trial contributes to the previously reported literature that ODS-CPM, which was thought to be incurable, can now have a chance of improvement of outcome using therapeutic plasma exchange.

Declarations:

Ethics Committee approval was sought before submission of this paper for possible publication. It is exempt from review because the data collection procedure did not involve more than minimal risk or harm to the patient; and, the information obtained was recorded in a manner to ensure that the patient cannot be identified.

The patient's family consented to medical reporting and publication of the patient's case.

The data and material are available at the Hospital Information Management Service of the Mariano Marcos Memorial Hospital & Medical Center, San Julian, Batac City.

The authors declare that they have no competing interests.

This study is author-funded.

All the authors form the patient's management team. SJP prepared the initial manuscript. All the authors read and approved the final manuscript.

The authors gratefully acknowledge the patient and his family for allowing us all to learn from his case and letting his story be told.

References

1. Mohan S, Gu S, Parikh A, Radhakrishnan J. Prevalence of hyponatremia and association with mortality: results from NHANES. *Am J Med* 2013;126(12):1127-37. e1. doi: 10.1016/j.amjmed.2013.07.021.
2. Aegisdottir H, Cooray C, Wirdefeldt K, Piehl F, Sveinsson O. Incidence of osmotic demyelination syndrome in Sweden: A nationwide study. *Acta Neurol Scand.* 2019;140(5):342-349. doi:10.1111/ane.13150.
3. Gagnon DG. Hyponatremia, osmotic demyelination syndrome, and the importance of the patient's history. *The Southwest Respiratory and Critical Care Chronicles* 2021; 9:45–53.
4. Changal KH, Raina H, Wani IY. Osmotic Demyelination Syndrome; Treated with Re Lowering of Serum Sodium. *Acta Neurol Taiwan* 2014;23(4):138-142.
5. Abdul Halim S, Mohd Amin NA. Treatment response in osmotic demyelination syndrome presenting as severe parkinsonism, ptosis and gaze palsy. *Case Reports* 2018;2018: bcr-2018-225751.
6. Yuridullah R, Kumar V, Nanavati S, Singhal M, Chandran C, Clinical Resolution of Osmotic Demyelination Syndrome following Overcorrection of Severe Hyponatremia. *Case Reports in Nephrology* 2019; Article ID 1757656, 4 pages, 2019. https://doi.org/10.1155/2019/1757656.
7. Wijayabandara, M., Appuhamy, S., Weerathunga, P., *et al.* Effective treatment of osmotic demyelination syndrome with plasmapheresis: a case report and review of the literature. *J Med Case Reports* 2021; 15:6. https://doi.org/10.1186/s13256-020-02573-9.
8. Bibl D, Lampl C, Gabriel C, Jungling G, Brock H, Kostler G: Treatment of central pontine myelinolysis with therapeutic plasmapheresis. *Lancet* 1999,353:1155.
9. Schuster, M, Diekmann, S, Volk, T. Central pontine myelinolysis despite slow sodium rise in a case of severe community-acquired hyponatraemia. *Anaesth Intensive Care* 2009; 37:117-20.
10. Grimaldi, D, Cavalleri, F, Vallone, S, Milanti, G, Cortelli, P. Plasmapheresis improves the outcome of central pontine myelinolysis. *J Neurol* 2005; 252:734–5.
11. Jameson, JL, Fauci, AS, Kasper, DL, Hauser, SL, Longo, DL, Loscalzo, J. Harrison's Principles of Internal Medicine, 20th Ed. McGraw-Hill Education, United States of America, 2018.
12. Anand, P, Zakaria, A, Benameur, K, Ong, C, Putman, M, O'Shea, S, Greer, D, Cervantes-Arslanian, AM. Myoclonus in Patients With Coronavirus Disease 2019: A Multicenter Case Series. *Crit Care Med* 2020Aug25:10.1097/CCM.0000000000004570.
13. Ahmed A, Asimi R, Sharma A, Nazir S. Diagnosis: Osmotic myelinolysis (central pontine myelinolysis and extrapontine myelinolysis). *Ann Saudi Med* 2007;27(4):308-311. doi:10.5144/0256-4947.2007.308.
14. Chang KY, Lee IH, Kim GJ, Cho K, Park HS, Kim HK. Plasma exchange successfully treats central pontine myelinolysis after acute hypernatremia from intravenous sodium bicarbonate therapy. *BMC Nephrol* 2014; 15:56. https://doi.org/10.1186/1471-2369-15-56.
15. Shemin D, Briggs D, Greenan M. Complications of therapeutic plasma exchange: a prospective study of 1,727 procedures. *J Clin Apher* 2007;22:270-6. doi:10.1002/jca.20143.
16. Kumon, S, Usui, R, Kuzuhara, S, Nitta, K, Koike, M. The Improvement of the Outcome of Osmotic Demyelination Syndrome by Plasma Exchange. *Intern Med* 2017; 56:733-6.