Plasmapheresis for Extrapontine Myelinolysis: A Case Series and a Literature Review

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Abstract
Central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) are syndromes of osmotic demyelination attributed to the rapid correction of hyponatraemia. Isolated EPM is a rare clinical entity which poses a significant diagnostic challenge especially in the absence of a rapid rise in sodium. Typical MRI findings aid in the diagnosis. Treatment for established osmotic demyelination syndrome (ODS) is nonstandardized and the prognosis is considered poor. Therefore, different strategies including plasmapheresis (TPE), immunoglobulins (IVIG), and steroids have been used. We present our findings from a series of successfully treated patients at a high-volume tertiary care center in Sri Lanka, with an appraisal of available literature. A total of 21 patients with established ODS are analyzed here, including 5 cases of EPM managed by the authors over a 2-year period. Thirteen (40.2%) patients were treated with plasmapheresis alone, 6 (28.5%) received dual therapy (TPE + IVIG or steroids) and 2 (9.5%) received triple therapy (TPE + IVIG + steroids). There was complete or near complete response in 18 (85.7%) and complete response in 10 (47.6%) patients. We conclude that although the management of CPM/EPM is largely symptomatic, patients may show a significant response to immunomodulatory therapy. The marked improvement in motor, cognitive, and functional domains supports an immune basis for osmotic demyelination. Plasmapheresis, in particular, leads to favorable outcomes in ODS which is supported by previously published case reports. We propose its utility as standard treatment.
Introduction

Central pontine myelinolysis (CPM) was first described in 1959 in alcoholics and malnourished individuals presenting with pseudobulbar palsy and quadriplegia [1]. Similar lesions were later identified regions such as the basal ganglia, thalami, and the cerebellum and termed extrapontine myelinolysis (EPM) [2]. These patients presented with disorders of movement and behavior. CPM and EPM together constitute the osmotic demyelination syndrome (ODS). Once the diagnosis is established clinically and radiologically, the overall prognosis is generally considered poor [2]. Management is supportive with no proven effective therapy. However, there are single case reports and small case series of successful treatment with steroids, intravenous immunoglobulin, and plasmapheresis. We report a case series of ODS from the Institute of Neurology, National Hospital of Sri Lanka from January 2019 to February 2021. We review 5 patients presenting with acute parkinsonism with varying degrees of brainstem dysfunction and their outcomes after management with plasmapheresis. We also summarize recent literature on plasmapheresis as therapy for this syndrome and propose this as a standard treatment option.

Case Series

Case 1

A 27-year-old man with no comorbidities presented with confusion and rigidity. He had several episodes of profuse vomiting 10 days back. He was admitted with drowsiness and was found to have a serum sodium of 105 mmol/L with a potassium of 4.4 mmol/L. Other routine bloods were normal. He was started on a hypertonic saline (3% NaCl) infusion, aiming at 8 mmol/L sodium correction per day with twice daily electrolyte monitoring. The sodium improved to 134 mmol/L over 7 days. During this period, he became agitated, confused, and rigid and was transferred to our tertiary care center for further management. There was no history of fever, seizures, or weakness. He had consumed alcohol occasionally. He had a BMI of 16.8 kg/m² and was afebrile. Cardiovascular, respiratory, and abdominal examinations were normal. Glasgow coma scale (GCS) was 12/15 (E-4, V-3, M-5). Tone was uniformly increased with cogwheel rigidity and asymmetrical upper limb tremor with monotonous speech. The remaining neurological examination was normal. Repeat serum sodium was 135 mmol/L. Biochemical investigations including osmolarity studies, glucose, and cortisol were normal. There was evidence of nonthyroidal illness with a TSH of 0.248 (0.55–4.78 IU), fT4-1.45 (0.89–1.79 IU), and fT3-1.7 (2.00–4.00 IU). His EEG, CSF studies, and noncontrast CT brain showed no abnormalities. MRI revealed bilateral symmetrical T2/FLAIR hyperintensities involving the caudate nucleus and putamen with sparing of the Globus pallidus (Fig. 1a). The lesions were hypo intense on T1 sequence with minimal contrast enhancement. There were no changes in the pons (Fig. 2b). A diagnosis of EPM was made based on the history and MRI findings. Later he went on to develop spastic quadripleasis with worsening tremors (Modified Rankin Scale [mRS] = 5). A repeat MRI showed myelinolysis temporally spreading to the pons (Fig. 2d). He was managed with five cycles of plasmapheresis and supportive therapy. On discharge, he was able to walk unaided with minimal residual tremor and rigidity (mRS = 1). An interval MRI done after 5 months showed clearing of lesions (Fig. 2e, f).

Case 2

A 62-year-old man, recently diagnosed with Parkinsonism presented with worsening extrapyramidal symptoms, three episodes of generalized tonic clonic seizures and confusion. He had no comorbidities and consumed alcohol daily. Six weeks prior to admission there had been an episode of subacute intestinal obstruction with repeated bouts of vomiting. On admission,
sodium had been 105 mmol/L with a potassium of 3.2 mmol/L. Sodium correction had been done with hypertonic saline over a period of 3 days to 132 mmol/L. He had then developed abnormal behavior with slowing of movements and upper limb tremors. Levodopa had been initiated, upon which tremor and bradykinesia had improved. On presentation to our center, he was afebrile, alert but confused with a GCS of 14/15 (E-4, V-4, M-6). He had bradykinesia and cogwheel rigidity with normal muscle power (MRS = 3). The remainder of the examination was unremarkable. At this point, serum sodium was 129 mmol/L, and potassium was 3.9 mmol/L. Other basic investigations were within normal limits. Urine and serum osmolarity studies, thyroid function tests, glucose, and serum cortisol were also normal. No abnormalities were detected on EEG, CSF analysis, or noncontrast CT of the brain. On MRI, there were T2/FLAIR hyperintensities (Fig. 1b) and T1 hypo-intensities with contrast enhancement of the caudate and putamen with pallidal sparing. The lesions were bilateral and symmetrical. The rest of the scan including the brainstem was normal. EPM was diagnosed. In addition to supportive therapy, he was treated with intravenous immunoglobulin 0.4 g/kg daily for 3 days and five cycles of plasmapheresis. Despite the delay in diagnosis, there was a marked improvement in symptoms, and the patient was fully oriented and ambulatory on discharge (MRS = 1).

**Case 3**

A 38-year-old man was admitted to the emergency department following a road traffic accident. His injuries included a mandibular fracture and a degloving injury to his right lower limb. On admission, there was no neurological deficit. Within 24 h of open reduction and

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**Fig. 1.** T2/FLAIR sequence MR scan of brain showing bilateral symmetrical basal ganglia hyperintensities with pallidal sparing (a) case 1 (b) case 2 (c) case 3 (d) case 5 (e), and case 4 (f) involvement of the pons in case 4.
Fig. 2. T2/FLAIR sequence MR scan of brain. **a** Typical basal ganglia hyperintensities at diagnosis. **b** Sparing of the pons at diagnosis. **c** Deepening of basal ganglia hyperintensities. **d** Involvement of the pons. **e** Clearing of basal ganglia hyperintensities. **f** Disappearance of pontine hyperintensity.
internal fixation of the mandibular fracture under general anesthesia, his GCS dropped to 10/15 (E-3, V-2, M-5). Examination revealed extrapyramidal rigidity and upper limb resting tremors, more prominent on the right side (MRS = 5). The surgery itself had been uneventful. However, there had been delayed recovery from anesthesia for which intravenous naloxone had been administered. His past medical history was significant for hypertension and obstructive uropathy. He was a nonsmoker and consumed alcohol occasionally. Throughout the course of the illness all electrolytes remained within the normal range (sodium- 141 mmol/L, potassium- 4.7 mmol/L, calcium- 2.1 mmol/L, magnesium- 1.09 mmol/L, phosphate- 2.2 mmol/L). The metabolic screen, including serum glucose was also normal. Although inflammatory markers were elevated (WBC 16.05 × 10^3 μL, CRP- 77 mg/L) CSF studies, EEG, and noncontrast CT brain were unremarkable. MRI revealed bilateral symmetrical T2/FLAIR hyper intensities of the caudate and the putamen with typical pallidal sparing (Fig. 1c). These areas were hypo intense on T1 sequence with contrast enhancement and the pons was spared. These findings together with the presence of extrapyramidal features confirmed a diagnosis of EPM. The patient was then managed with 5 cycles of plasma exchange in addition to levodopa. A good recovery was seen with his GCS improving to 15/15 and gradual reduction of extrapyramidal symptoms over a period of 6 weeks (MRS = 2).

Case 4
A 24-year-old previously healthy woman presented at 9 weeks of gestation with repeated episodes of nausea and vomiting over 1 month and altered consciousness for 1 day. A diagnosis of hyperemesis gravidarum was made. Hyponatremia of 113 mmol/L and hypokalemia of 2.7 mmol/L had been noted and corrected with intravenous 3% saline and KCl infusions. The sodium had risen to 127 mmol/L over 48 h. Despite correction of electrolyte abnormalities, her GCS deteriorated to 8/15 over 24 h, and she developed spastic quadriparesis. All basic biochemical investigations and inflammatory markers were within normal ranges with a normal noncontrast CT brain. A lumbar puncture was performed which revealed cyto-protein dissociation with a cerebrospinal fluid protein value of 103 mg/dL. A presumptive diagnosis of autoimmune encephalitis was made on day 8 of symptom onset. The patient was given daily intravenous methylprednisolone 1 g for 3 days without significant improvement. She was then transferred to our tertiary care center for further evaluation. Upon admission, she had a GCS of 9/15 (E-4, V-1, M-4) and was quadriparetic. She had rigidity and exaggerated reflexes with upgoing plantars. Dystonic limb posturing was also noted (MRS = 5). Cranial nerve examination including ophthalmoscopy was normal. Serum sodium on transfer was 136 mmol/L. An urgent MRI brain was performed with MR angiography and venography. This revealed hyperintensities in the pons as well as in the basal ganglia with no evidence of venous sinus thrombosis (Fig. 1d, e). A diagnosis of ODS was made. Unfortunately, she had a miscarriage for which she underwent evacuation of retained products of conception under general anesthesia. Following the surgery, the patient was initiated on therapeutic plasma exchange every other day for a total of 5 cycles approximately 3 weeks after symptom onset. After 1 month of hospital stay, there was some improvement in alertness and swallowing (MRS = 4). She was referred for intensive physiotherapy.

Case 5
A 53-year-old man with triple vessel disease was admitted for coronary artery bypass graft surgery. Preoperative investigations were unremarkable apart from a sodium of 116 mmol/L. Although the patient was asymptomatic, sodium correction was done by withholding diuretics and addition of oral salts prior to surgery. The sodium rose to 124 mmol/L within 24 h and to 136 mmol/L after another 24 h. The surgery was successfully completed, and the patient was transferred to the high dependency unit for postoperative monitoring. On
postoperative day 2, the patient’s wife noted mild slurring of speech and slowing of movements. Over the next 3 days, he developed tremor and rigidity with marked reduction in speech and mobility. He was started on levodopa-carbidopa and discharged after cardiac management was complete. Due to persistence of neurological deficits, he presented to our center for expert opinion. On presentation, he had marked extrapyramidal rigidity and was unable to walk or communicate adequately (MRS = 4). MRI of the brain revealed T2 signal hyperintensities in the basal ganglia with sparing of the Globus pallidus typical of EPM (Fig. 1f). He was started on a regime of every other day plasmapheresis based on our previous experience. At the end of 5 cycles, he had significant improvement in speech and motor skills. He was able to walk with assistance at the end of 1 week. Follow-up at 2 months found him to be walking without assistance and able to attend to his basic care independently (MRS = 2).

**Literature Review**

**Demographics**

Sixteen similarly treated patients were identified and reviewed. The findings are summarized in Table 1. Ten (62.5%) were female, and six (37.5%) were male. The mean age was 46 (±14.8) years. Five (31.25%) patients reported a history of chronic alcohol abuse, four (25%) patients developed ODS following orthotopic liver transplantation, one (6.25%) had a history of anorexia, and background details were unavailable in six (37.5%) cases. All patients had CPM confirmed by imaging. Two (12.5%) patients had EPM in addition to CPM. Prior to development of ODS, eleven (68.75%) patients had severe hyponatremia (Na+ <120 mmol/L) and two (12.5%) had moderate hyponatremia (Na+ 120–125 mmol/L). The majority (76.9%) have had rapid correction. CPM was also demonstrated after rapid hypernatremia correction [5, 7]. Three patients developed ODS in the absence of sodium over correction.

**Treatment**

All patients we reviewed were treated with therapeutic plasma exchange. Ten (62.5%) patients received plasmapheresis alone, four (25%) received plasmapheresis followed by intravenous immunoglobulin (IVIG) and two (12.5%) received triple therapy with plasmapheresis, IVIG, and intravenous methylprednisolone. Seven (43.75%) patients were treated within 1 week of symptom onset, whereas treatment initiation was delayed beyond 2 weeks in five (31.25%) patients. The longest gap from symptom onset to treatment was 23 days, reported in 2 patients. The time from presentation to treatment initiation was not reported in 4 (25%) cases. The dosage of plasmapheresis ranged from 3,840 mL to 37,300 mL, and the dose of IVIG was 0.4 g/kg.

**Outcomes**

Eight (50%) patients had complete motor recovery following treatment. Five (31.25%) patients were able to walk without assistance and one (6.25%) patient walked with assistance. The authors reported suboptimal treatment response in two (12.5%) patients. Both patients had treatment initiated beyond 2 weeks of symptom onset.

**Discussion**

ODS is an uncommon disorder with significant morbidity and mortality. Prevention takes precedence as there are no standardized treatment protocols. The use of plasmapheresis as a treatment option has previously been documented in 13 case reports (Table 1). We have summarized our own experience in Table 2.
### Table 1. Summary of previous reports of plasmapheresis used for ODS

| References        | Age and sex | Background | Initial Na⁺ | Presence of rapid correction | Syndrome | Time from onset to treatment, days | Treatment | Dosage                          | Outcome                        |
|-------------------|-------------|------------|-------------|------------------------------|----------|----------------------------------|-----------|---------------------------------|---------------------------------|
| Bibl et al. [3]   | 29 yr, F    | CAA        | 107         | Yes                          | +        | Immediate                        | TPE       | 24,700 mL                      | Complete motor recovery         |
|                   | 20 yr, F    | Anorexia   | 105         | No                           | +        | Immediate                        | TPE       | 5,243 mL                       | Walk without assistance         |
|                   | 30 yr, F    | CAA        | N/A         | No                           | +        | Immediate                        | TPE       | 18,270 mL                      | Complete motor recovery         |
| Grimaldi et al. [4]| 59 yr, F    | CAA        | 113         | Yes                          | +        | Immediate                        | TPE       | 37,300 mL                      | Walk without assistance         |
| Saner et al. [5]  | 64 yr, M    | Post liver transplant | 136 | No                           | +        | N/A                              | TPE       | 24,000 mL                      | Walk without assistance         |
| Ludwig et al. [6] | 51 yr, M    | Post liver transplant | 125 | No                           | +        | 2                                | TPE       | 21,870 mL                      | Complete motor recovery         |
|                   | 54 yr, F    | Post liver transplant | 115 | No                           | +        | 2                                | TPE       | 17,097 mL                      | Walk without assistance         |
| Chang et al. [7]  | 40 yr, F    | Post liver transplant | 142 | No                           | +        | N/A                              | TPE       | 4,394 mL                       | Walk without assistance         |
| Kumon et al. [8]  | 71 yr, F    | Post liver transplant | 101 | Yes                          | +        | 23                               | TPE       | 3,840 mL                       | Complete motor recovery         |
| Rebedew [9]       | 34 yr, M    | CAA        | 109         | Yes                          | +        | 6                                | IVIG, TPE, IVIG | N/A                              | Complete motor recovery         |
| Atchaneeyasakul et al. [10] | 63 yr, M | Post liver transplant | 128 | Yes                          | +        | 19                               | TPE, IVIG | 5 days                         | Suboptimal response             |
| Mahmood et al. [11]| 50 yr, F   | Post liver transplant | 99  | Yes                          | +        | 20                               | TPE       | 7 cycles                       | Complete motor recovery         |
| Krishnan et al. [12]| 55 yr, F   | Post liver transplant | <100 | Yes                          | +        | N/A                              | TPE       | 5 cycles                       | Complete motor recovery         |
| Nelson et al. [13]| 23 yr, F    | Post liver transplant | 118 | Yes                          | +        | 14                               | TPE       | 15,500 mL                      | Suboptimal response             |
| Eze et al. [14]   | 49 yr, M    | CAA        | 102         | Yes                          | +        | N/A                              | TPE       | 6 cycles                       | Walk with assistance            |
|                   |             |            |             |                              |          |                                  | IVIG, TPE, IVIG | 125 mg 8 hourly for 3 days    |                                |
| Wijayabandara et al. [15] | 43 yr, M | Post liver transplant | 97  | Yes                          | +        | 23                               | TPE       | 11,132 mL                      | Complete motor recovery         |
The mean age of the patients we treated was 40.8 (±14.8) years, similar to previously reported cases. In ODS, CPM is more commonly encountered and may occur with EPM. Isolated EPM occurs in about two-fifths of cases. Interestingly, all patients that we encountered had EPM and 2 patients had both EPM and CPM. Extrapyramidal features are often masked by involvement of the pyramidal tracts and the brain stem. Acute onset parkinsonism is most often seen in cases of isolated EPM as demonstrated in the majority of our patients. We emphasize that EPM should be included in the differential diagnosis of rapid onset extrapyramidal symptoms regardless of the electrolyte status.

The diagnosis of ODS is supported by characteristic findings on MR imaging which includes bilateral symmetrical T2 hyperintensities and hypo-intensities on T1 weighted imaging. These lesions are usually noncontrast enhancing and may show diffusion restriction on DWI sequencing [2]. The characteristic “trident sign” is seen in the pons in CPM while EPM changes have been described in the basal ganglia, white matter, and cerebellum. Pallidal sparing is a specific feature of EPM that distinguishes it from other conditions involving the basal ganglia [2]. These changes were present in our patients and are presented in Figure 1.

The aetiological link between osmotic demyelination and overcorrection of hypernatremia is well established. The sudden rise in serum osmolality may supersede the brain’s osmoregulatory mechanisms, leading to shrinkage of neurons, resulting in demyelination and oligodendrocyte apoptosis [2]. It is of interest to note that four (80%) of our patients developed ODS in the absence of hyponatremia with 1 patient (case 3) having neither hyponatremia nor rapid correction. This highlights the other contributory factors like alcoholism and malnutrition [2]. We identified chronic alcohol abuse in 1 patient (case 2) and chronic malnutrition in another (case 1).

Plasmapheresis is hypothesized to reduce high-molecular weight myelin-toxic substances released by osmotic stress [7]. The immune basis to ODS is supported by the excellent response to plasmapheresis. Interestingly, we observed a remarkable recovery in a patient treated after 6 weeks of symptom onset (case 2). However, this patient had comparatively mild symptoms. Our only patient who had suboptimal response (case 5) was treated beyond 2 weeks of diagnosis and had both pontine and extrapontine involvement.

### Conclusion

Plasmapheresis has been successfully used as treatment for ODS. Given the practical difficulties of conducting a randomized controlled trial, recommendations for practice must be based on case reports and series. Additional difficulties arise as negative outcomes are under-reported. The majority of cases we managed, as well as the reported cases, showed excellent treatment responses. Immunoglobulin and steroids have also been used successfully. However,
evidence remains limited as to which treatment regime is superior. We also identified a few reports of suboptimal outcomes. The common factor observed was a delay in treatment initiation. We conclude that there is ample ground to recommend plasmapheresis within the first 2 weeks of diagnosis of ODS. Adjunctive immunomodulatory therapy may be used as per clinician preference.

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Statement of Ethics

Informed consent was obtained from all the patients. The patients have given their written informed consent to publish their case (including publication of images). The paper is exempt from Ethical Committee approval as it does not meet the DHHS definition of “research.”

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the conception or design of the work; the acquisition, analysis, and interpretation of data for the work; and drafting the work. They all approved the final draft to be published. All authors agree to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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