EJCRIM
European Journal
of Case Reports
in Internal Medicine

# THE RESPONSE OF OSMOTIC DEMYELINATION SYNDROME TO PLASMAPHERESIS IN A PATIENT PRESENTING WITH CATATONIA AFTER CORRECTION OF HYPONATRAEMIA IN HYPEREMESIS GRAVIDARUM

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**Received:** 09/02/2024 **Accepted:** 19/02/2024 **Published:** 11/03/2024

**Conflicts of Interests:** The Authors declare that there are no competing interests.
**Patient Consent:** Written informed consent was obtained from the patient for publication of this case report and accompanying images.


**How to cite this article:** Rangsrisaeneepitak V, Tekarnjnavanit A, Kanjanapipatkul P, Koowattanatianchai S. The response of osmotic demyelination syndrome to plasmapheresis in a patient presenting with catatonia after correction of hyponatraemia in hyperemesis gravidarum. *EJCRIM* 2024;**11**:doi:10.12890/2024_004373.

## ABSTRACT

Osmotic demyelination syndrome (ODS) is a disorder characterised by the widespread development of demyelination in both pontine and extrapontine regions. It has been recognised as a complication arising from the rapid correction of hyponatraemia. This study presents the case of a 20-year-old Thai female patient at 10 weeks gestation, exhibiting an initial presentation of catatonia – an uncommon manifestation of ODS. The patient developed symptoms following the rapid correction of hyponatraemia in the context of hyperemesis gravidarum. Magnetic resonance imaging (MRI) of the brain revealed a trident or bat-wing-shaped pattern in T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences at the central pons. The patient underwent five cycles of plasmapheresis and received rehabilitation, leading to clinical improvement.

## KEYWORDS

Osmotic demyelination syndrome, catatonia, hyponatraemia, hyperemesis gravidarum, plasmapheresis

## LEARNING POINTS

- Osmotic demyelination syndrome (ODS) is a rare but potentially devastating neurological complication, such as catatonia, resulting from the correction of hyponatraemia.
- Pregnancies complicated by hyperemesis gravidarum tend to exhibit hyponatraemia and hypokalaemia, which serve as contributing risk factors for ODS.
- Plasmapheresis is considered as an option in the treatment of ODS for the removal of inflammatory substances.

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## INTRODUCTION

Osmotic demyelination syndrome (ODS) is a syndrome caused by oligodendrocyte apoptosis and shrinkage without inflammation[1]. It was first clinically and histologically described in alcoholic and malnourished patients by Adams and Victor in 1959[2]. The most common cause of ODS results from the rapid correction of hyponatraemia in the patient with certain risk factors. Risk factors include malnutrition, chronic alcoholism, hypokalaemia, hypophosphataemia, and reported in pregnancy with hyperemesis gravidarum[3,4]. Here, we present a case of ODS that occurred after the correction of hyponatraemia with an 3% hypertonic saline solution in a pregnant woman with hyperemesis gravidarum and concomitant hypokalaemia, which are additional risk factors for the development of this syndrome.

## CASE DESCRIPTION

We report the case of a 20-year-old pregnant woman at 10-week gestation who was admitted to our hospital due to severe vomiting. She had no past medical history and denied alcohol consumption. The clinical examination revealed moderate dehydration with normal blood pressure and an increased heart rate. Her blood sodium level was 107 mmol/l, and potassium was 2.2 mmol/l. She was diagnosed with hyperemesis gravidarum, accompanied by hyponatraemia and hypokalaemia. She was treated with intravenous 3% hypertonic saline solution along with metoclopramide and oral potassium chloride elixir. On the following day the symptoms improved with an elevation in sodium levels to 120 mmol/l (a rise of 13 within 22 hours), while potassium levels increased to 3.0 mmol/l. The attending physician administered intravenous isotonic NaCl solution and prescribed oral potassium chloride elixir on the second day. She was hospitalised for four days and then discharged. Before discharge, her blood sodium level was 128 mmol/l, and the potassium level was 3.4 mmol/l. The timeline for sodium and potassium correction is detailed in *Figure 1*.

On the fourth day after the initial admission, the patient returned to the emergency department because her father noticed that she was uncooperative and drowsy. Upon readmission, she exhibited aggressive and inappropriate behaviour, such as walking naked in the ward. Additionally, she developed abnormal hyperkinetic movements characterised by generalised stiffness and slowing of the body, including catalepsy and waxy flexibility. She also exhibited reduced eye blinking, posturing and difficulty in speaking – a condition known as catatonia. The physical examination revealed that she was fully conscious but agitated, with a slow response to simple commands and severe spastic dysarthria. Rigidity was noted in all extremities, and sensory and cerebellar signs could not be evaluated. Other systemic examinations were unremarkable. Further investigations were conducted, revealing blood chemistry results that indicated a sodium level of 127 mmol/l and a potassium level of 3.0 mmol/l. A lumbar puncture was performed on the same day. Open pressure was 14 cm$H_2O$, and closed pressure was 12 cm$H_2O$.

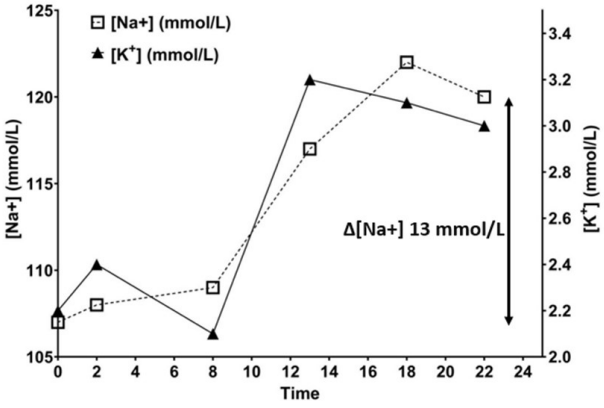


*Figure 1. Timeline for sodium and potassium correction.*

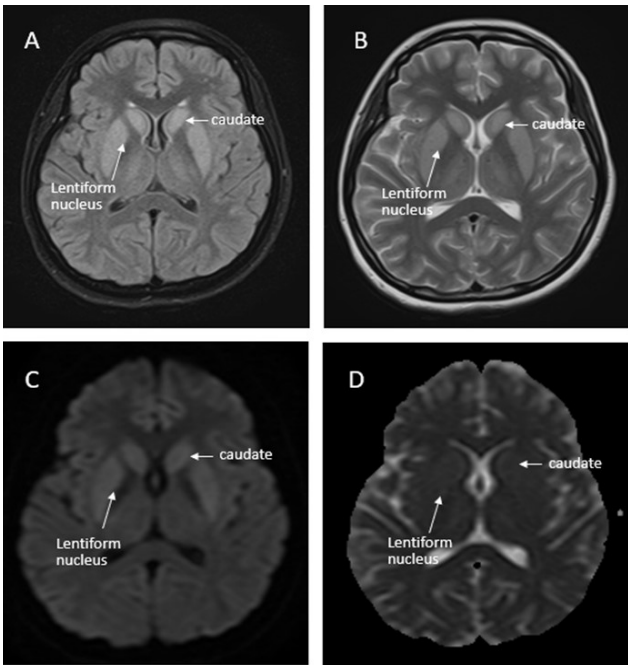


*Figure 2. The magnetic resonance imaging (MRI) of the brain (A: T1-weighted showed bilateral hyposignal intensity, B: T2-weighted showed bilateral hypersignal intensity, C: diffusion-weighted imaging (DWI) showed high signal intensity D: apparent diffusion coefficient (ADC) showed low signal intensity) at caudate and lentiform nuclei.*

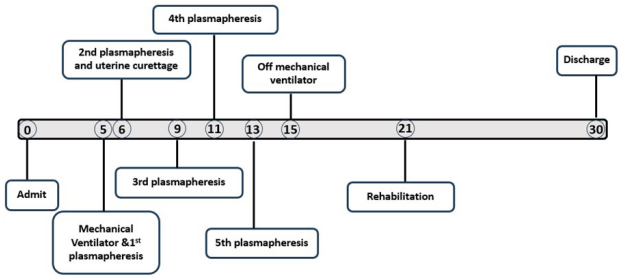


*Figure 3. The clinical course of the patient.*

The cerebrospinal fluid (CSF) showed no pleocytosis, a normal sugar ratio and a mild elevation in protein. CSF culture and blood culture showed no bacterial growth. The viral, autoimmune and paraneoplastic panels were also negative.

The magnetic resonance imaging (MRI) of the brain revealed symmetrical hypersignal intensity in T2-weighted,

hyposignal intensity in T1-weighted and restricted diffusion in diffusion-weighted imaging (DWI) / apparent diffusion coefficient (ADC) at the caudate and lentiform nuclei *(Fig. 2)*. These observations are indicative of findings consistent with extrapontine myelinolysis (EPM).

The symptoms of catatonia were treated symptomatically with tizanidine and benzodiazepine; however, catatonia still persisted. Five days later, the patient developed high-grade fever, dyspnoea, and desaturation, and was diagnosed with aspiration pneumonia. Endotracheal intubation was needed, and she was put on a mechanical ventilator. Intravenous antibiotics (piperacillin/tazobactam) were prescribed, along with sedation. The obstetrician was consulted to assess the condition of her foetus, revealing an absence of foetal heart sounds. Consequently, the physician decided to proceed with uterine curettage and we discussed further treatment options with her parents and husband. A decision was reached to initiate plasmapheresis. After the first cycle of plasmapheresis, the symptoms of catatonia did not improve, so we initiated the second cycle the next day. There was minimal partial improvement in the symptoms of rigidity, but we could not take her off the mechanical ventilator. The third, fourth and fifth cycles of plasmapheresis were performed later. The day after the fifth cycle the spasticity had significantly improved, and we were able to take her off the mechanical ventilator. She then underwent a physical therapy programme and rehabilitation to increase her range of motion and reduce her spasticity. She was discharged on day 30 after admission with residual dysarthria and demonstrated the ability to transfer using a wheelchair. The clinical course of this patient is shown in *Figure 3*.

We performed an MRI of the brain two weeks after the onset of catatonia, which revealed the presence of the trident sign at the mid-pons, a classical manifestation indicative of central pontine myelinolysis (CPM) *(Fig. 4)*. Nevertheless, no clinical signs of quadriparesis were observed. After a follow-up at four weeks in the outpatient department, she could ambulate with minimal external support. Additionally, clinical catatonia, dysarthria and abnormal behaviour had disappeared.

## DISCUSSION

In pregnant women, ODS may occur following the rapid correction of hyponatraemia, a condition that can be observed in hyperemesis gravidarum, as in the case described here. In addition to severe hyponatraemia, this patient also concurrently presented with hypokalaemia, which is an additional factor that may enhance susceptibility to ODS[3]. The mechanism by which hypokalaemia leads to ODS is unclear, but some propose that hypokalaemia induces a reduction in the quantity of Na-K ATPase within vascular endothelial cells and oligodendrocytes, rendering these cells more susceptible to osmotic stress[5]. A physiological consequence of a normal pregnancy is an increased susceptibility to hyponatraemia, attributed to hormonal alterations, augmented blood volume and dietary factors. Furthermore, hyponatraemia is exacerbated by the presence of hyperemesis gravidarum[6].

The onset of symptoms began 4 days after the overcorrection of sodium, a phenomenon typically observed within a range of one day to two weeks [1,7]. Clinically, ODS may present with various neurological signs and symptoms, depending on the severity of involvement and the affected areas. Approximately 50% of cases manifest as isolated CPM, while the remaining cases are more or less evenly divided between isolated EPM and a combination of CPM and EPM, with a slight prevalence of the latter condition [8], which aligns with our case.

Here, the patient presented with disinhibition and emotional lability, followed by catatonia on the next day, which is not very common. Catatonia is a syndrome comprising psychiatric and motor symptoms, with some considered pathognomonic signs including verbigeration, catalepsy, waxy flexibility and echophenomena[9]. Catatonia in EPM has been infrequently reported, and all cases indicate striatum involvement[10]. The MRI findings of the brain at the onset of the disease are consistent with EPM. An interesting point is that the classic signs of CPM appeared after two weeks without any preceding clinical signs. Case reports of ODS in pregnancy with hyperemesis gravidarum have been reviewed and are listed in *Table 1*.

An MRI of the brain is the gold standard imaging technique to reveal ODS lesions. These include hypointense T1-weighted lesions and hyperintense lesions demonstrated on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. Classic imaging in CPM shows a trident or bat-wing shape at the central pons[1]. In EPM, the pattern differs; it typically involves the cerebellum, lateral geniculate body, basal ganglia, thalamus and cerebral cortex, exhibiting symmetrical hyperintensity in T2-weighted sequences[1].

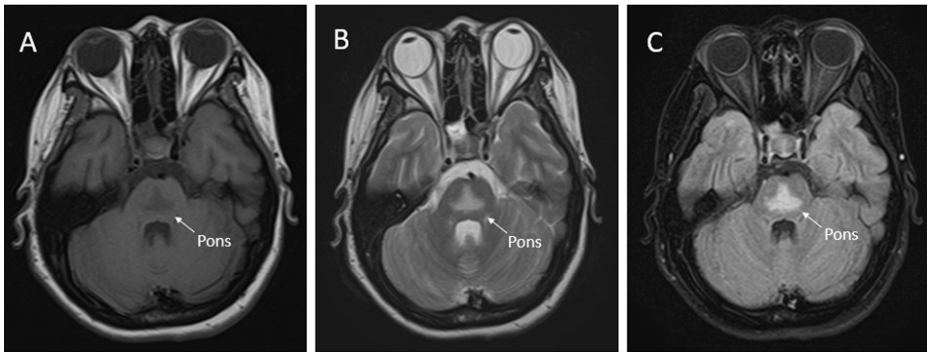


*Figure 4. The magnetic resonance imaging (MRI) of the brain (A: T1-weighted showed hyposignal intensity, B: T2-weighted showed hypersignal intensity, C: fluid-attenuated inversion recovery (FLAIR) image showed hypersignal intensity) at the mid-pons.*

| Reference | Age (years) | GA (weeks) | Na+ (mmol/l) | K+ (mmol/l) | ODS symptoms (onset from sodium correction) | Imaging | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|
| Fraser, 1988[15] | 18 | 19 | 126 to 145 (in 48h) | 2.3 | Spastic quadriparesis with a spastic dysarthria (10 days) | CPM | Intravenous thiamine 250 mg | A deficit of short-term memory, residual spastic dysarthria and truncal ataxia |
| Corona et al., 2014[6] | 21 | 10 | 107 to 124 (in 24h) | 1.1 | Restless and confused (24 hours) | EPM | Intravenous steroids | Ambulates with minimal external support |
| Janga et al., 2015[16] | 42 | 14 | 125 to 132.2 (in 24h) | 2.9 | Psychomotor retardation, intention tremor, fluctuating altered mental status and incontinence (14 days) | CPM | Slowly corrected with hypotonic solution administration | Ambulates with minimal external support |
| Anand et al., 2017[17] | 23 | 16 | 120 to 129 (in 24h) | 2.3 | Spastic quadriparesis (4 days) | CPM | Supportive treatment | No neurological deficit |
| Ian et al., 2018[18] | 32 | 14 | 109 to 123 (in 15h) | 1.7 | Neuropsychiatric manifestations and lower limb weakness (4 days) | CPM, EPM | Intravenous methylprednisolone for 5 days | Ambulates with minimal external support |
| Rodríguez-Pinto et al., 2020[19] | 35 | 12 | 127 to 135 (in 22h) | 2.4 | Catatonia, lockjaw and psychosis (30 days) | EPM | Supportive treatment | Residual neurological symptoms requiring assistance for ADL |
| Salim et al., 2021[20] | 19 | 14 | 127.7 to 135 (in 48h) | 2.0 | Depression with catatonia and aphasia (2 days) | CPM, EPM | Intravenous methylprednisolone for 3 days | Residual catatonia requiring assistance for ADL |

Abbreviations: GA, gestation age; ODS, osmotic demyelination syndrome; CPM, central pontine myelinolysis; EPM, extrapontine myelinolysis; ADL, activities of daily living.

*Table 1. Literature review of ODS in pregnancy with hyperemesis gravidarum.*

The treatment of ODS remains controversial. Louis et al[11] reported the long-term outcome in ODS patients, showing that 31% died and 31% required life-supporting therapy after one year of follow-up. There are likely cases that are thought to be incurable or irreversible, in which physicians still use conservative treatment after diagnosing ODS. However, there are few case series reporting positive outcomes with plasmapheresis[12,13], which particularly emphasise performing plasmapheresis within 5 days after symptoms begin, as was done in our case. Notably, the symptoms have been shown to recover within a few days after the last session of plasmapheresis[12-14], which aligns with our case. Additionally, plasmapheresis is considered an effective treatment for chronic ODS. A case report by Kumon[14] demonstrated complete recovery from ODS when plasmapheresis was initiated on the 39$^{th}$ day of hospitalisation. This finding supports the notion that ODS does not spontaneously recover with supportive treatment alone. Osmotic stress, immunologic reactions, inflammatory cytokines and myelinotoxin production are postulated to be part of ODS pathophysiology; therefore, plasmapheresis removes these substances, leading to clinical improvement[12-13].

## CONCLUSION

ODS represents an iatrogenic complication, specifically arising from the rapid correction of severe hyponatraemia. Recognising the individualised risk factors in each patient and carefully monitoring blood sodium stands as a pivotal aspect in preventing ODS. Catatonia is one of the clinical presentations that is infrequent. In addition to symptomatic and supportive treatments, consensus is lacking on definitive treatment. Nonetheless, there is supportive evidence for the efficacy of plasmapheresis in improving neurological outcomes.

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