

Impressive clinical improvement of severe osmotic demyelination syndrome: A clinical image

Julien Rousseau, Nicolas Greciet, Alby Richard

CASE REPORT

We present the case of a 58-year-old woman who was transferred to our academic institution from a peripheral hospital for suspected osmotic demyelination syndrome (ODS). Past medical history was notable for hypertension, alcohol use disorder, and major depressive disorder. Her medications included hydrochlorothiazide, paroxetine, quetiapine, and lorazepam. In terms of habits, she consumed on average 8 alcoholic beverages per day, in addition to being a 35-pack-year smoker. She reported poor eating habits with decreased caloric intake during the weeks preceding her hospitalization, but she continued to consume alcohol and to take her medications as prescribed, including her thiazide diuretic. Notably, her antidepressant dose had been increased two weeks prior from 10 to 20 mg daily.

She was brought to the emergency room of the peripheral hospital for five days of worsening confusion, dizziness, tremors, and gait imbalance that had led to several falls. Physical and neurological examination demonstrated an altered sensorium with disorientation and inattention, tremors, lower extremity spasticity with bilateral clonus at the ankles and ataxic gait. Initial laboratory investigations showed a serum sodium concentration of 106 mmol/L with hypokalemia and

metabolic alkalosis. A head computed tomography (CT) performed on the same day showed no acute intracranial abnormalities. She was given 3% sodium chloride in an effort to improve her acute neurological symptoms. Her hyponatremia was corrected to 117 mmol/L within less than 24 h, and was further increased up to 136 during the following week (Table 1).

Table 1: Serum sodium concentrations during hospitalization

| Date (2021) | Serum sodium concentration (mmol/L) | Medical intervention |
|------------------|-------------------------------------|--|
| 01/19 (3:00 PM) | 106 | IV ^a NaCl 3% |
| 01/19 (10:00 PM) | 109 | IV NaCl 3% |
| 01/20 (8:00 AM) | 117 | IV NaCl 3% |
| 01/21 | 122 | IV NaCl 3% |
| 01/22 | 127 | |
| 01/23 | 129 | Reg. ^b lorazepam |
| 01/24 | 129 | Reg. lorazepam |
| 01/25 | 130 | Reg. lorazepam |
| 01/26 | 130 | |
| 01/27 | 133 | |
| 01/28 | 136 | ICU ^c consultation IV desmopressin |
| 01/29 | 129 | IV desmopressin |
| 01/30 | 114 | IV desmopressin |
| 01/31 | 121 | IV desmopressin |
| 02/01 | 127 | |
| 02/02 | 134 | |

Serial serum sodium concentration values in mmol/L with corresponding dates and interventions from the treating team. ^aIntravenous, ^bRegular, ^cIntensive care unit.

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Received: 07 June 2022

Accepted: 26 August 2022

Published: 15 September 2022

On the fifth day of hospitalization, the patient started deteriorating. She could no longer walk unassisted due to severe truncal ataxia, became increasingly confused, and developed worsening tremors and dysarthria. Alcohol withdrawal was suspected, and she was prescribed benzodiazepines. On day 9, the patient was transferred to the intensive care unit for depressed level of consciousness and was intubated. Magnetic resonance imaging (MRI) of the brain (nine days after initial presentation) showed an area of restricted diffusion in the central pons, consistent with osmotic demyelination syndrome (Figure 1). In an attempt to prevent further cerebral injury, intravenous desmopressin was administered, re lowering her serum sodium concentration (Table 1). She was then transferred to our center and remained in the neurological intensive care unit, where she developed a ventilator-associated pneumonia and underwent percutaneous tracheostomy. Within two days after sedation was weaned the patient progressively regained consciousness, and was eventually transferred to the neurology ward, where she underwent intensive rehabilitation. A follow-up brain MRI at five weeks demonstrated chronic injury to the central pons, as well as signs of diffuse extrapontine demyelination (Figure 2). On the day of discharge to an inpatient rehabilitation facility she displayed moderate residual cognitive deficits, dysarthria, severe gait ataxia, and persistent spastic paraparesis which required walking aids. Twelve months later, the patient had regained full autonomy and reported a complete resolution of her dysarthria and walking difficulties.

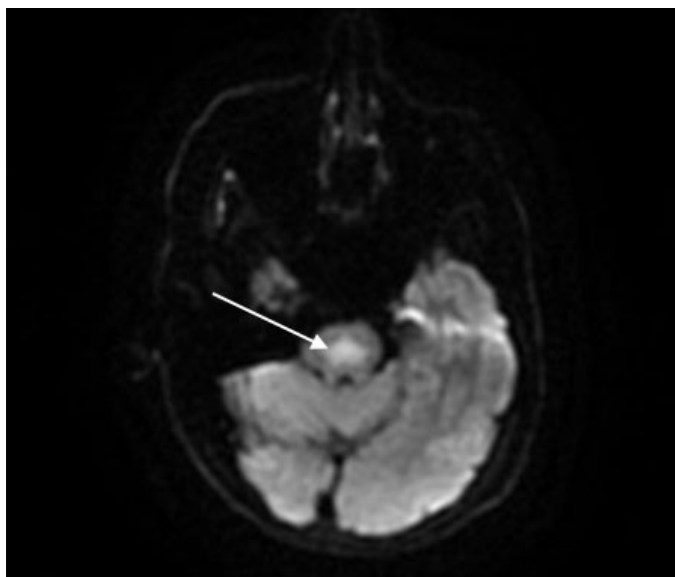


Figure 1: Brain diffusion-weighted magnetic resonance imaging (MRI) performed four days after symptom onset with hyperintense changes delineating a zone of early demyelination within the central pons (arrow).

DISCUSSION

The neurological sequelae due to overrapid hyponatremia correction are referred to as osmotic

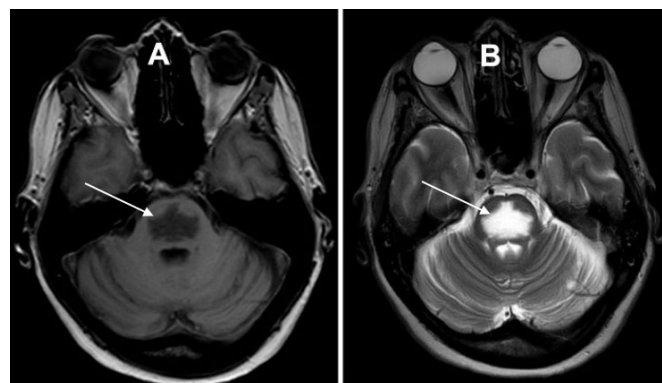


Figure 2: (A) T1 and (B) T2 brain MRI performed five weeks after symptom onset showing respectively marked hypointense and hyperintense changes to the central pons (arrows) measuring 2.3×1.5 cm and indicating a region of severe axonal destruction as a result of ODS.

demyelination syndrome. Although it is a well-known phenomenon, its true incidence is unknown. Sodium is the main contributor of serum osmolality. In order to prevent pathological shifts in free water between the intracellular and extracellular compartments, the hypothalamus maintains serum osmolality between 135 and 142 mmol/L through thirst stimulation and antidiuretic hormone release from the posterior pituitary gland [1]. Whereas sodium can freely cross capillaries throughout the body, the blood brain barrier is impermeable to sodium, making the central nervous system prone to injury from extreme changes in serum osmolality. Hyponatremia is the most common electrolyte disorder and is defined as serum sodium concentration of less than 135 mmol/L. Abnormally low serum sodium values create an osmotic gradient which leads free water to cross from the serum into astrocytes. In the acute phase, this precipitates cellular edema and cell wall lysis [2]. Initially, neurological symptoms of hyponatremia are often nonspecific and include malaise, fatigue, confusion, headaches, and muscle cramps. Further water influx into astrocytes, and eventually neurons, causes seizures, coma, neurogenic pulmonary edema, increased intracranial pressure, herniation, and death [1].

The brain has developed compensation mechanisms to serum hypoosmolality in order to prevent such events from occurring. As a means of increasing extracellular osmolality, astrocytes and neurons release electrolytes, mainly potassium, as well as organic osmolytes, including taurine, myo-inositol, glycine, glutamate, and aspartate [3]. This phenomenon takes approximately 48 hours to complete, which is why abrupt hyponatremia can cause severe neurological impairment, whereas chronic hyponatremia (developing over more than 48 h) often presents asymptotically. Chronic intracellular hypotonicity resulting from the completion of these adaptive processes renders brain cells particularly sensitive to rapid correction of hyponatremia and can lead to ODS [2].

The pathophysiology of ODS is not fully understood. It is believed that extreme osmotic gradients during hyponatremia overcorrection lead to astrocytic death in particularly vulnerable brain regions due to cellular water loss and influx of cations intracellularly. Decreased trophic stimulation of oligodendrocytes, inflammation, and microglial inflammation eventually leads to apoptosis and demyelination [4]. Brain regions that are the slowest at recuperating previously excreted solutes are the most susceptible to demyelination [5]. The pons is most commonly involved (central pontine myelinolysis), but concurrent extrapontine involvement is commonly reported with the cerebellum, midbrain, thalamus, and basal ganglia being frequently affected [6, 7].

Osmotic demyelination syndrome occurs commonly in patients with chronic and severe hyponatremia (120 mmol/L or less) who undergo rapid correction serum sodium correction. Other risk factors include concurrent hypokalemia, alcoholism, malnutrition, cirrhosis, liver transplant, and severe burns [6, 8]. Osmotic demyelination syndrome often has a biphasic clinical course: patients initially present with symptomatic hyponatremia, after which rapid serum sodium correction may lead to a period of symptomatic improvement. This is often followed by neurological deterioration due to myelinolysis, usually within seven days of serum sodium correction [8]. The most common symptoms of central pontine involvement include flaccid leading to spastic quadriparesis, dysarthria and dysphagia. Extrapontine disease can lead to a variety of movement disorders, with Parkinsonism being the most commonly described [2]. Other symptoms of ODS include seizures, confusion, lethargy, locked-in state, and coma [1].

The diagnosis of ODS is based on clinical and paraclinical elements (i.e., laboratory results), as well as on imaging characteristics. Magnetic resonance imaging is the most sensitive modality and shows lesions that are hyperintense in T2-weighted imaging and fluid-attenuated inversion recovery (FLAIR) and hypointense in T1-weighted imaging, which represents vasogenic edema linked to disruption of the blood brain barrier [9]. Diffusion-weighted imaging (DWI) abnormalities are common. Magnetic resonance imaging changes can be delayed and repeat imaging is advised if ODS is suspected clinically [7]. The *trident sign*, a characteristic MRI finding in ODS, represents a hyperintense area on T2-weighted imaging (or hypointense area on T1-weighted imaging) within the central pons with sparing of the ventrolateral pons including the corticospinal tracts (Figure 3) [10]. The distribution of the anomalies and the predominant changes within the central pons are thought to be related to a high oligodendrocyte concentration and tightly arranged crossing white matter tracts and grey matter [9].

Historically, ODS has been associated with a poor prognosis. However, recent publications report clinical resolution in a significant proportion of patients. In a French retrospective study of 36 patients with ODS, 31%

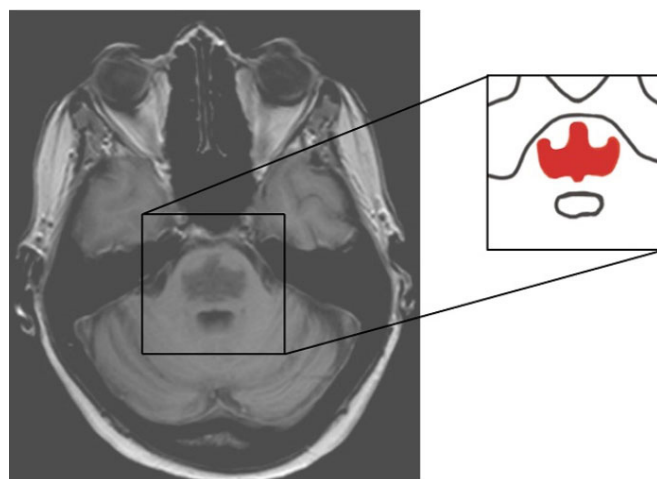


Figure 3: Trident sign in osmotic demyelination syndrome: hypointense changes on T1 within the central pons.

died and 56% returned to a functioning level corresponding to a modified Rankin score of 1 or less [11]. Interestingly, illness severity did not predict long-term outcomes. Once the diagnosis of ODS is established, the mainstay of treatment is supportive. In patients who underwent correction of hyponatremia beyond the recommended thresholds, there is a general recommendation to relower serum sodium concentration to prevent further demyelination. This is typically accomplished by administering intravenous desmopressin in order to bring the serum sodium concentration back within the 6 mmol/L per 24 h target. Importantly, this treatment recommendation, based on limited observational data, is largely theoretical and merits future research [12].

Avoiding overcorrection of hyponatremia is crucial for the prevention of ODS, and is predicated on prompt treatment of hyponatremia in patients with severe neurological symptoms to prevent further cerebral edema and death. This should be accomplished by administering 3% sodium chloride with the aim of raising the serum sodium concentration by 4–6 mmol/L over 1 h [8, 12]. Chronic hyponatremia should be corrected slowly, at a rate of 4–8 mmol/L per day, with an even stricter goal of 4–6 mmol/L per day in patients with known risk factors for ODS [8].

Our patient had multiple risk factors for ODS, including alcohol use, malnutrition, severe hyponatremia, and concomitant hypokalemia at presentation. She developed severe neurological deficits leading to coma and mechanical ventilation requirements. Her MRI displayed typical signs of ODS with significant changes within the central pons and multiple areas of extrapontine demyelination at five weeks as described above. Her full return to a baseline functional status, although surprising considering the severity of her initial presentation and radiological changes, is in keeping with the often unexpected course of ODS previously described [11]. The attempt at relowering her serum sodium concentration to

a mild level of hyponatremia might have contributed in slowing the progression of demyelination, although this practice has not been studied in randomized controlled trials. Recently, immunomodulatory treatments including plasmapheresis have been used successfully in patients with ODS, underlying inflammation as a possible contributor to demyelination [13].

CONCLUSION

In conclusion, ODS is a potentially catastrophic, preventable, and mostly iatrogenic complication of rapid correction of chronic hyponatremia. We presented a unique case in that our patient had a surprising return to baseline neurological function despite a severe initial presentation and extensive demyelinating changes on imaging. This reinforces the concept that the severity of illness at presentation is not a reliable predictor of long-term outcomes. Further observational studies are needed to determine reliable prognostic factors, and to refine certain elements of the treatment algorithm. Identification of hyponatremic patients at risk for ODS is key, and serum sodium correction should be accomplished slowly with a maximal increase of 6 mmol/L per 24 h in individuals who are most predisposed. Protocolized order sets could be considered as a means of preventing hyponatremia overcorrection, and ensure standardized, evidence-based approaches to negate needless injury and complications.

Keywords: Central pontine myelinolysis, Magnetic resonance imaging, Osmotic demyelination syndrome

How to cite this article

Rousseau J, Greciet N, Richard A. Impressive clinical improvement of severe osmotic demyelination syndrome: A clinical image. *Int J Case Rep Images* 2022;13(2):113–117.

Article ID: 101339Z01JR2022

doi: 10.5348/101339Z01JR2022CI

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Author Contributions

Julien Rousseau – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Nicolas Greciet – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Alby Richard – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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