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Centropontine Myelinolysis after Conservative Correction of Hyponatremia: A Case Report and Review of Contributing Factors

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Abstract

Introduction: Centropontine myelinolysis (CPM) is a rare pathology, a delayed neurological complication corresponding to massive demyelination of the protrusion. Its exact pathogenesis is poorly understood. Rapid correction of sodium hyponatremia has been implicated as a potent causative factor. We report a case of CPM despite a priori conservative correction of hyponatremia with a favorable course in a 61-year-old alcoholic-smoker diabetic. **Case Presentation:** A 61-year-old man with chronic alcoholism presented to the emergency department (D0) with physical asthenia and anorexia. He was treated for severe hyponatremia at 104 mmol/L by careful rehydration with saline before being transferred to a nephrological hospital. Magnetic resonance imaging (MRI) performed at D14 for locked-in syndrome showed osmotic demyelination syndrome (Figure 1). The evolution was favorable after 3 months of rehabilitation marked by a progressive and clear improvement of clinical signs. **Conclusion:** This observation suggests an evaluation of the benefit/risk ratio of the short-term prognosis of profound hyponatremia with that of the metabolic stress induced by a still too rapid correction. Particular attention should be paid to diabetic patients in the context of chronic alcoholism or nutritional deficiencies.

Keywords

Centropontine Myelinolysis, Hyponatremia, Alcoholism

1. Introduction

Centropontine myelinolysis (CPM), also known as osmotic demyelination syndrome (ODMS), is a rare condition and a dreaded neurological complication corresponding to massive demyelination of the protuberance [1]. According to several anecdotal reports, this condition results from the rapid correction of severe hyponatremia [2]. The exact pathogenesis of ODMS is poorly understood [3].

CPM has been described in many conditions, especially in alcoholic, diabetic and malnourished patients [4]. It can rarely occur without fluid and electrolyte disturbances in chronically alcohol-dependent patients [5].

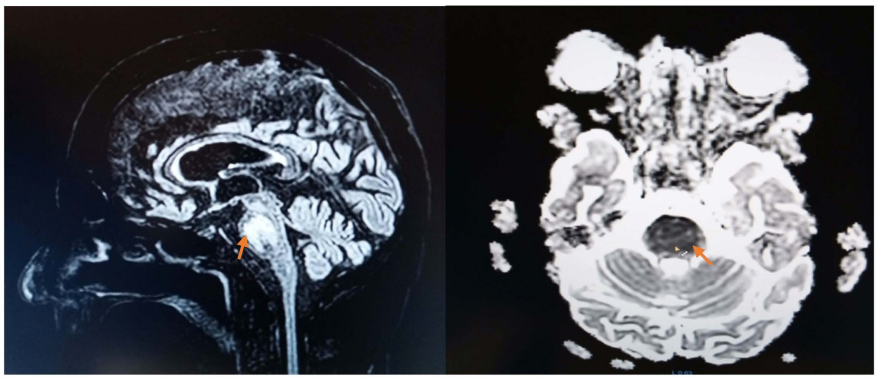
While PCM was originally considered to be uniformly fatal, evidence now shows that a significant number of patients can have some neurological recovery even with severe symptoms at the outset [6].

We report a case of CPM despite an a priori conservative correction of hyponatremia with a favourable evolution in a 61-year-old diabetic alcoholic-smoker.

2. Case Presentation

A 61-year-old man presented to the emergency department (D0) with physical asthenia and anorexia. He had a few episodes of arterial hypotension at home 3 days before. His history included essential hypertension on irbesartan associated with hydrochlorothiazide (COAPROVEL® 300/25mg), type II diabetes on repaglinide and chronic alcoholism and active smoking.

The patient was hemodynamically stable on admission to the emergency room and the biological work-up showed severe hyponatremia at 104 mmol/L, kalemia at 4.3 mmol/L, and chloremia at 66 mmol/L. The calculated plasma osmolarity



(a) (b)

Figure 1. (a) Flair hypersignal area (area of oedema) at the central part of the circular bridge (arrow); (b) Diffusion hypersignal area with a round central ADC drop (arrow).

was 243 mOsm/L. The protidemia was 77 g/L, the albuminemia was 36 g/L, and the alcohol level was 0.9 g/L. The urine ionogram showed natriuresis at 19 mmol/L, kaliuresis at 49 mmol/L and urine osmolarity at 358 mOsm/L.

The creatinine level was 98 µmol/L for a baseline creatinine level of around 100 µmol/L. Thyroid and adrenal axis investigations were normal.

The initial treatment consisted of an infusion of 2 liters of 0.9% isotonic saline with 5 g of sodium (infusion rate not specified) with an increase in natraemia of 2 mmol/L in 24 hours before being transferred to the nephrology department for further management.

The physical assessment revealed a blood pressure of 140/68 mmHg, a temperature of 37˚C, a heart rate of 89 beats per minute, a weight of 90 kg, a height of 180 cm and a body mass index of 22.78 cm/kg^2. The patient was clinically euvolemic. The neurological examination was normal with a Glasgow score of 15/15.

In a second phase, hyponatremia was gradually corrected (**Figure 2**), with cautious rehydration with saline and water restriction. He was also given vitamin B1, B6 and diazepam to prevent alcohol withdrawal syndrome.

The evolution was marked by a progressive deterioration of the neurological state from day 9 onwards with the onset of apathy and confusion. The electroencephalogram and brain scan did not reveal any acute abnormalities. At the same time, an infectious syndrome appeared with no clear point of call. In search of the origin of the infectious syndrome, the chest X-ray did not show any parenchymal focus. The lumbar puncture (LP) showed a clear cerebrospinal fluid (CSF), a protein level of 0.92 g/L, a glucorachy of 1.66 g/L and a sterile culture. Similarly, the urine cytobacteriological study (UCS), 2 sets of blood cultures, and the COVID-19 test were negative. A probabilistic antibiotic therapy based on cefotaxime was administered.

The magnetic resonance imaging (MRI) was performed at D14 in the face of the onset of progressive flaccid tetraplegia, and a Glasgow score of 8. It showed a T2, FLAIR and diffusion hypersignal with ADC restriction of the centre of the protuberance associated with dilatation of the ventricular system and cortical sulci in favour of an osmotic demyelination syndrome (**Figure 1**).

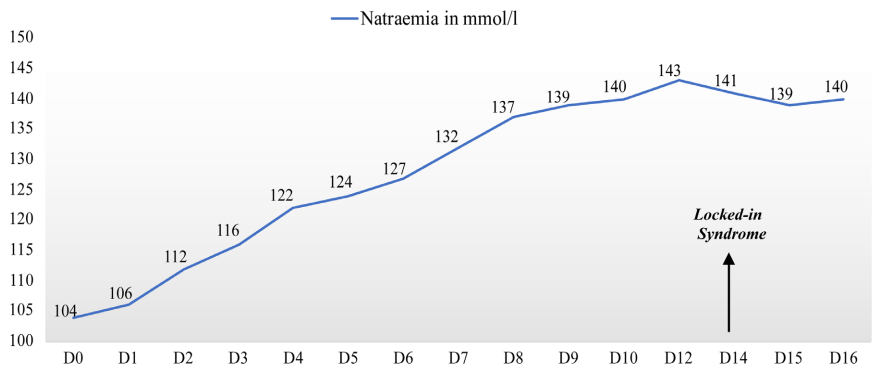


Figure 2. Evolution of hyponatremia correction.

The neurological picture was associated with diabetic decompensation and acute renal failure (ARF).

The patient was transferred to a general intensive care unit where he was intubated, ventilated and sedated with a Glasgow score of 3 under sedation and areflexia of all 4 limbs. Pupils were reactive intermediates with normal gasometry under 50% FiO_2 in spontaneous ventilation. Hemodynamics required mild norepinephrine support. Vascular filling and insulin therapy by electric syringe were instituted. In view of the increase in ARF (creatinine level of 437 µmol/L versus 98 µmol/L) despite vascular filling, continuous veno-venous haemodiafiltration (CVVHDF) was instituted with citrate anticoagulation. The AKI resolved with complete normalisation of renal function after 3 days of CVVHDF.

The state of consciousness progressively improved until normal consciousness was regained on day 20 of his transfer to intensive care. A gastrostomy tube was placed for a few episodes of false routes despite effective swallowing.

In terms of infection, a second LP was carried out and showed a clear CSF with no other notable anomalies. The UCS showed a male urinary infection with K. pneumoniae, treated with ertapenem.

Neurologically, the electromyogram showed a significant peripheral neuropathy of the axon-myelin type in the lower limbs, probably related to alcoholic neuropathy.

After 1 month in an intensive care unit, the patient was transferred to a follow-up and rehabilitation hospital. The evolution at 2 months was marked by an effective resumption of oral feeding, fluent speech and initiation of standing. After three and a half months of rehabilitation, a progressive and clear improvement in neurological signs was noted; language had become more fluent with more or less autonomous walking with the help of a walker. He was discharged from the follow-up and rehabilitation care facility 4 months later.

3. Discussion

ODMS including centropontine and extrapontine myelinolysis was first described in 1959 by Adams [7] in alcoholic and malnourished patients. The actual incidence of this condition is unknown to this day [7] [8]. The exact pathophysiology of ODMS is uncertain. Ashrafian and Davey [9] have proposed an attractive hypothesis that glial cell apoptosis is the main cause of myelinolysis lesions. One suggestion is that sodium-coupled amino acid transporters (SNAT2) are down-regulated by hypotonia, delaying the return of osmolytes to the brain, making them more sensitive to correction of hyponatremia. Although serum Na^+ and K^+ return to normal within a few hours, osmotically active solutes in the brain require several days to reach normal levels. This temporary imbalance causes cerebral dehydration and can lead to a potential breakdown of the blood-brain barrier. Astrocytes appear to be an early target of the disease, leading to their activation of microglial cells and the expression of pro-inflammatory cytokines [10].

The CPM can occur at any age with a rather polymorphic clinical expression. It may even remain silent, discovered by chance during brain imaging [11]. The neurological signs classically occur in a delayed manner after a free interval of 1 to 6 days after correction of hyponatremia, manifesting as a change in behaviour, cranial nerve palsies, progressive weakness leading to quadriplegia and even a Locked-in Syndrome [12].

In our case, the patient progressively presented from D7 - D8 of the correction of hyponatremia with apathy and confusion. The brain scan and electroencephalogram did not show any acute abnormalities.

The brain scan is not very sensitive for the diagnosis. Brain MRI is the radiological examination of choice, showing a hypersignal area on T2 and FLAIR weighted sequences, hyposignal on T1 weighted sequences. The onset of these abnormalities is usually delayed by 10 to 15 days. An initially normal MRI does not rule out the diagnosis [13].

In our patient, the MRI was performed on day 14 and clearly showed that it was a centropontine myelinolysis.

Other possibly confounding pathologies, notably stroke and meningitis, had been ruled out by the CT scan and the CSF study. Proteinorrachia on CSF study was also suggestive of CPM [14].

Although the aetiology of CPM remains unclear, rapid correction of serum sodium in the context of chronic hyponatraemia has been implicated as a strong causative factor [7]. Recently, evidence has begun to accumulate suggesting that additional factors are also significant in the pathogenesis of this condition [15] [16] [17]. **Table 1** summarises the risk of neurological complications in patients with hyponatraemia [10].

There is no validated curative treatment. It is essentially based on symptomatic measures, such as the gentle and progressive correction of hydroelectrolytic disorders, particularly hyponatremia, and the insertion of a gastric tube or, better still, a feeding jejunostomy and vitamin therapy. More specific resuscitation measures are indicated in case of respiratory disorders and the contribution of corticosteroid therapy is discussed. Prevention remains essential and is based on progressive correction of deep hyponatremia without exceeding a correction rate of 0.5 mmol/L per hour with multi-day monitoring of natraemia [4].

Table 1. Risk of neurological complications in patients with hyponatremia.

Acute cerebral oedema	*Osmotic demyelination syndrome* (*centropontine myelinolysis*)
- Postoperative menstruation - Female subject - Elderly women taking thiazides - Patients with secondary polydipsia - Hypoxemic patients - Marathon runners	- Liver transplant patients - Alcoholic patients - Patients with malnutrition - Hypokalaemic patients - Elderly women taking thiazides - Hypoxemic patients - Severe hyponatremia below 105 mmol/L*.

*The risk factors identified in our case.

In the past, CPM was originally considered to be uniformly fatal. Nowadays, evidence shows that a significant number of patients can have some neurological recovery, even with the severe symptoms at the beginning [18].

In a series reported by George *et al.* [15], five of nine patients with osmotic demyelination had apparent neurological recovery. Almost all patients in this cohort with incident OMDS had a documented episode of rapid correction of hyponatremia.

In our case, we were dealing with a patient with chronic alcoholism in whom the CPM occurred on day 14 after correction of hyponatremia that was reasonably assumed to be less than 0.5 mmol/L/h according to the literature [6].

The evolution was favourable after 3 months of rehabilitation marked by a partial recovery of the neurological lesions with sequelae of dysarthria and mild cognitive disorders.

This recovery comes at the cost of a long period of rehabilitation as evidenced by this observation.

4. Conclusion

In this review, we suggest that the etiology of CPM may be multifactorial, related in part to glial and neuronal osmotic stress, attributable to both profound hyponatremia and/or its rapid correction. Particular attention should be paid to people with well-recognised metabolic defects, such as chronic alcoholism or nutritional deficiencies. In terms of prognosis, the short-term benefit/risk ratio of even profound hyponatremia should be assessed against that of the metabolic stress induced by a still too rapid correction.

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Conflicts of Interest

The authors declare that they have no competing interests.

Consent for Publication

Informed consent was obtained from the trusted person.

Authors' Contributions

ASF, CB, AG diagnosed, treated and clinically monitored the patient. ASF conducted the literature search and wrote the manuscript. MS, SBC, SS, HY, CM, AK, NC and SF reviewed the manuscript. HDY reviewed the MRI images.

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Abbreviations

CPM: Centropontine Myelinolysis, D: Day, ODMS: Osmotic Demyelination Syndrome, MRI: Magnetic Resonace Imaging, AFR: Acute Renal Failure, LP: Lumbar Puncture, CSF: Cerebrospinal Fluid, UCS: Cytobacteriological Study, CVVHDF: Continuous Veno-Venous Haemodiafiltration.