Osmotic demyelination affecting extrapontine areas of brain

Uduman Ali Mohamed Yousuf, Heng Siang Ting, BM Yashodhara, Shashikiran Umakanth

ABSTRACT

Introduction: Inappropriate fluid management in sick patients has a rare potential consequence called osmotic demyelination syndrome (ODS); either central pontine myelinolysis (CPM) or extrapontine myelinolysis (EPM) or combination of both. As reported in the studies, the incidence of these varies from 0.05–5.7% as per the different autopsy studies. The clinical presentation is variable from “Locked in syndrome” to seizures, behavioral and personality changes.

Case Report: A 58-year-old ADL (activities of daily living) independent, apparently healthy, social and friendly female presented with aggressive behavior, excessive talking and disorientation after being treated for vomiting and diarrhea in a hospital. All these symptoms and events occurred after initial treatment for pneumonia. Her CT scans of brain were normal and had normal blood reports on thorough assessment.

Conclusion: Prompt evaluation with EEG and MRI scan clinched the diagnosis of osmotic demyelination syndrome (ODS). We report one such presentation in the patient who had complete recovery at one year of follow-up.

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CASE REPORT

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one such presentation in the patient who had complete recovery at one year of follow-up.

Keywords: Behavioral disturbance, Extrapontine area of brain, Osmotic demyelination, Sodium

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INTRODUCTION

Osmotic demyelination syndrome (ODS), presenting either as central pontine myelinolysis (CPM) or extrapontine myelinolysis (EPM) or combination of both, is a rare non-inflammatory demyelination disorder involving pons and other areas of brain and occurs as a consequence of rapid correction of hyponatremia. It was renamed later when the pathologic findings of central pontine myelinolysis (symmetric area of myelin disruption) was also found in extrapontine area [1]. In a study done in Japan, out of 1000 consecutive autopsies done, of which 626 brains were examined, 37 cases were found, giving rise to the incident rate of 5.7% [2]. In a different larger scale retrospective study that was conducted, the incidence rate was found to be 0.05% (15 cases in over 3000 autopsies done). Clinically, asymptomatic CPM found at autopsy has always been at least as frequent as cases diagnosed premortem and serves as a reasonable indicator for the incidence of the disease [3].

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CASE REPORT

A 58-year-old female, apparently healthy retired kindergarten teacher, was referred to the hospital for aggressive behavior, non-stop and irrelevant talking and reduced sleep for 3–4 weeks. There were no known medical illness except for thyroidectomy 20 years back and hypertension. She was ADL independent, not ill-tempered social and friendly before the onset of the illness and has many friends, as revealed by her daughter. Prior to this incident, the patient had fever, cough with yellowish sputum production for a few days, for which she was treated in a private hospital with i.v. antibiotics. Later, while she was still in the private hospital, she had profuse vomiting and diarrhea for one week. She received i.v. antibiotics, i.v. fluids, i.v. anti-emetics and i.v. pantoprazole during her stay hospital. A week after her stay in the hospital, she had an episode of tonic movements, developed blank stare and CT brain was done and it was reported as normal except for mild cerebral atrophy (Figure 1). She was moved from general ward to intensive care unit, in that hospital, in view of these developments while diarrhea and vomiting resolved. She was observed for one more week in general ward before she was discharged. She required sedation to sleep during her stay in that hospital as noted by the daughter. At discharge from that hospital, the patient would talk incoherently. During her stay at home for two weeks, the patient was able to feed and dress herself, and she could, recognize family members in the beginning. Two weeks after discharge patient developed symptoms of sleeping difficulties, abusive behavior and physical aggression. The day before admission to our hospital the patient needed to be physically restrained at home. There was no history of rash, neck pain, headache, UTI symptoms and memory disturbances.

Past history: Apparently healthy after thyroidectomy 20 years back. She has been on treatment for hypertension, had no history of psychiatric, neurological disorder or any drug allergy in the past. There was no history of recent travel to other places or jungle trekking.

The patient was married and had four children and all were healthy.

On examination the patient was restless, talks incoherently, answers only a few questions, no eye contact, not oriented to time, place and person, Glasgow coma scale was: E4, V4 M5. There was no neck stiffness and Kernig's sign was negative. There were no rashes on skin. Cardiovascular, respiratory and abdominal examinations were normal. Central nervous system reflexes were increased bilaterally and planters were down going. Power: Normal in all limbs. There were no cranial nerves palsies, no cerebellar signs. Repeat CT scan of brain done in the emergency department was normal. Neurologist was consulted and a possibility of Herpes simplex/encephalitis was considered. All the listed differentials, as mentioned in Table 1, were systematically ruled out.

Figure 1: Computed tomography scan of brain: Normal except for mild cerebral atrophy and mild dilation of lateral ventricles.

Table 1: List of differential diagnoses

- Acute delirium
- Meningoencephalitis
- Herpes simplex encephalitis
- Seizures with post epileptic confusion
- Metabolic encephalopathy
- Intracranial Space occupying lesions
- Dementia with delirium
- Stroke

On reviewing the reports from previous private hospital it was found that she had received IV augmentin 1.2 g BD for 5 days, IV azithromycin 500 mg OD for 3 days for pneumonia. Workup for *Legionella* and *Mycoplasma* were negative. We also noted from the previous hospital records that she had severe hyponatremia (sodium 107 mEq/L), following vomiting and diarrhea. During admission to that hospital her serum sodium was found to be rapidly normalized to 128 mEq/L in 24 hours by i.v. 3% saline (▲ 21 mEq/L) and also, she received i.v. ceftriaxone 1 g BD for 5 days for diarrhea and for altered sensorium. We did not find serum osmolality and urine osmolality reports from previous hospital; however, these were normal in the present admission at our hospital. In view of these findings, an EEG and MRI brain scan were done. EEG showed bilateral cerebral dysfunction with

excessive bilateral frontotemporal beta wave activity and MRI scans were suggestive of osmotic demyelination syndrome; T1 weighted MRI scans showed bright signals over basal ganglia and hippocampus on both sides. Also, there were hyperintense areas over right occipital and right parietal lobes (Figure 2). T2-weighted scans showed hyperintense signals over basal ganglia and swollen hippocampus bilaterally (Figure 3). Her serum sodium reports were normal after discharge from previous private hospital. The cause of severe hyponatremia was probably due to severe vomiting and diarrhea. She was not on hydrochlorothiazide, did not have hypothyroidism, primary polydipsia, cortisol deficiency, renal disease or SIADH as revealed by investigations.

Figure 2: T1-weighted magnetic resonance imaging scan showed bright signals over basal ganglia and hippocampus on both sides. There are hyperintense areas over right occipital and right parietal lobes. There is a periventricular hyperintensity representing probably previously existing microvascular changes.

Figure 3: T2-weighted magnetic resonance imaging scan showed hyperintense signals over basal ganglia and swollen hippocampus bilaterally.

Investigations

Full blood count, routine urine examination, LFT, RFT, CRP, ESR, serum calcium, serum magnesium, and ABG were normal. Serum sodium, urine and serum osmolality were normal. CT scan of brain was normal (Figure 1). Blood glucose levels were normal. Hepatitis B, C and HIV tests were negative. EEG showed bilateral cerebral dysfunction with excessive bilateral frontotemporal beta wave activity. The MRI scan of brain (Figures 2 and 3): showed features consistent with osmotic demyelination in extrapontine locations in frontotemporal areas. Investigations for the cause of hyponatremia were also done. Her Thyroid function tests and morning serum cortisol were normal.

Treatment

She received neurobion, amlodipine and resperidone tablets, while she was in hospital. The family was counseled and subsequently the patient was followed in neurology outpatients department.

Outcome and follow-up

- She was under neurologist's follow-up in the outpatients department. Three months after discharge on the said medications (vide supra) sleep was normal, patient was alert, walks without support, not aggressive in behavior, but talks irrelevantly.
- Six months after the discharge, the patient was able to sleep well, ADL independent, cheerful. The daughter was happy with the improvements.
- Ten months after discharge patient had fully recovered.
- One year after the discharge, the patient is completely normal.

DISCUSSION

Osmotic demyelination syndrome most frequently occurs in adults, [4] but multiple cases have also been reported in children [5]. There are many associations between ODS and other medical conditions like alcoholic, [1] liver transplant, [4] end stage renal diseases, [6] and burn patients (Table 2) [7]. However, the striking similarity found between all is a rapid change in serum osmolality, mainly due to an over rapid correction of hyponatremia, [7, 8] typically followed an elevation in serum sodium > 20 mEq/L/24 hours, [9] although rarely it had been reported to be associated with hypokalemia, [10, 11] ODS is a consequence of a hyperosmotically induced demyelination-[1]. Its exact pathophysiology is poorly understood, but an experiment mainly involving hyponatremia in rats led to the hypothesis that osmotic injury caused by over rapid correction of hyponatremia is the main cause ODS. Most of the change of brain osmolality in chronic hyponatremia can be accounted by

Table 2: Causes of hyponatremia

Hypovolumic causes:
• Dehydration
• Vomiting
• Diarrhoea
• Diuretics
Hypervolemic causes:
• Congestive heart failure
• Cirrhosis of liver
• Nephrotic syndrome
Euvolemic causes:
• SIADH
Other causes:
• Beer drinking/Chronic alcoholism
• Sertraline
• Lithium

the changes in organic osmolytes and brain electrolytes; and rapid correction of hyponatremia is associated with an overshoot of brain sodium and chloride levels along with a low organic osmolyte level. The high cerebral ion concentrations in the absence of adequate concentrations of organic osmolytes may be relevant to the development of central pontine myelinolysis [12, 13]. The clinical features of ODS typically range in severity from mild and transient confusion to severe spastic quadriparesis, pseudobulbar palsy, and impairment in the level of consciousness [9]. Rarely, in the cases where central pons are involved, patients can present as 'locked in syndrome'. Extrapontine involvement however can present with psychiatric symptoms like catatonia, hallucinations, behavioral or personality change can easily lead to a misdiagnosis [1]. Moreover, it can be difficult to diagnose because the onset of clinical features can be delayed for 2–6 days after rapid correction of hyponatremia, [9, 14] as in our patient. High index of suspicion is needed to make a diagnosis especially if a patient with normal electrolytes presents with neurological complaints long after correction and previous history of rapid correction of hyponatremia may not be clearly evident, exemplified in our case study. Diagnosis is made with imaging studies mainly MRI scan, where myelinolysis lesions can be found at pontine or extrapontine areas [15]. The lesions appear hyperintense on T2-weighted and FLAIR MRI images. These lesions do not enhance with GDTA. In our case, the demyelinations were found in extrapontine areas. EEG may show non-specific slow wave activity consistent with metabolic disorder as in our case. CT scan can be used occasionally to diagnose ODS with its typical hypodense lesions in pons, [16] however has been largely replaced by MRI scan due to the higher sensitivity [17]. It may take as long as 4 weeks for MRI scan to become positive after disease onset [15] hence making it worthwhile to repeat neuroimaging studies 10–14 days to confirm diagnosis. Latest technique of diffusion-weighted imaging has an advantage of earlier diagnosis whereby patient could be diagnosed within 24 hours of onset of symptoms [18]. Since there is no established treatments for ODS

other than supportive management, [1] prevention becomes the mainstay of treatment. Rate of correction of hyponatremia needs to be closely regulated, especially in case of chronic hyponatremia and severe hyponatremia at time of presentation. The proposed rate of correction of hyponatremia is <8 mmol/L per 24 hours [19] and <12 mmol/L in 48 hours [20]. In terms of more careful and forethought approach as reported by the recently published "expert panel recommendations" would be to restrict the elevation of serum sodium to 4–6 mmol/L in 24 hours [20]. In case if there is any inadvertent elevation of serum sodium more than above recommended values does occur, re-induction of hyponatremia could be done by using intravenous 5% dextrose or desmopressin or combination of both. Other pharmacological approaches to prevent the myelin damage following over-correction of hyponatremia could be usage of any one the agents; corticosteroids, intravenous immunoglobulin, plasmapheresis, minocycline, urea and myoinositol. Besides, these measures physical therapy and symptomatic treatment could be used [20]. In our case, re-induction of hyponatremia was not done, as there was a gap of 3–4 weeks after rapid hyponatremia correction had happened in previous hospital. Only correct diagnosis, symptomatic treatment, family counseling and physical therapy were offered to the patient in our hospital. The prognosis is not that grave as in olden times of first recognition of this condition in mid-1970s. Mortality as low as 6% and recovery as high as 40% was reported in 44 German patients with ODS [20].

CONCLUSION

The formulae that are used to calculate and correct the serum sodium in hyponatremia are not accurate in replenishing dynamically changing serum sodium in a patient. The prevention of osmotic demyelination syndrome (ODS), central pontine myelinolysis (CPM) or extrapontine myelinolysis (EPM) can be done by frequent monitoring of serum sodium and its gradual correction. Close and frequent monitoring of serum sodium is vital in the prevention of ODS.

Author Contributions

Uduman Ali Mohamed Yousuf – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Heng Siang Ting – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Yashodhara BM – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Shashikiran Umakanth – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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