Occurrence of osmotic demyelination syndrome in diabetes mellitus: A case report and literature review of various etiologies for osmotic demyelination syndrome

Sushil Kumar Yadav1, Rajeev Ojha2, Naresh Parajuli3, Susmin Karki1, Sobin Pant1, Ragesh Karn2, Bikram Prasad Gajurel2, Reema Rajbhandari2, Niraj Gautam2, Ashish Shrestha2 and Anamika Jha4

Abstract
Osmotic demyelination syndrome is a rare condition reported mainly in the case of rapid correction of hyponatremia, but it can occur even in the case of complicated diabetes mellitus either during rapid correction of hyperglycemia or anytime during the complicated diabetes mellitus. We report a case of complicated diabetes mellitus developing osmotic demyelination syndrome. The patient had presented with altered sensorium and seizure, which was initially diagnosed as hyperglycemia, but during his treatment, the magnetic resonance imaging of brain revealed central pontine myelinolysis. Our search on the causes of osmotic demyelination syndrome other than rapid correction of hyponatremia has revealed several other causes like autoimmune liver disease, Sjogren’s syndrome and non-Hodgkin’s lymphoma in addition to diabetes mellitus.

Keywords
Central pontine myelinolysis, diabetes mellitus, osmotic demyelination syndrome, complicated diabetes mellitus

Introduction
Osmotic demyelination syndrome (ODS) is non-inflammatory demyelination of neurons due to apoptosis of oligodendrocytes and infiltration of myelin degrading macrophages. Based on location of demyelination, ODS is classified into central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM).1,2 ODS is a rarely reported disease, and studies have shown its prevalence of about 0.06% among all hospitalized patients. Despite being rare, it is a serious issue which can even lead to severe disability or death. ODS is usually reported in cases of chronic alcohol use, alcohol withdrawal and rapid correction of hyponatremia.1 ODS in case of diabetes mellitus (DM) has not got as much concern in literature as in case of hyponatremia although DM seems to be a significant cause of ODS. We report a rare case of ODS with CPM which has complicated DM as underlying cause.

Case description
A 24-year-old male, who is a known case of type II DM for 5 years, presented with loss of consciousness, abnormal behaviour (shouting and aggressiveness), four episodes of seizure and altered sensorium for 5 days. The first seizure

1135595

SCO

DOI: 10.1177/2050313X221135595

journals.sagepub.com/home/sco
A sudden onset of jerking of upper and lower limbs with loss of consciousness occurred 5 days back while he was lying on bed and talking with his family members. There was uprolling of eyes with frothing of saliva; however, no tongue bite or incontinence was found. Patient's consciousness was regained after 10 min, but drowsiness persisted for about 30 min. A similar second seizure episode repeated next day with patient remaining unconscious for about 40 h. He was admitted to our center for further management. He had altered sensorium. He had two further attacks of seizures on the fourth and fifth days. He had severe retinopathy with neovascularization of the iris. Pan-retinal photocoagulation was planned for the treatment of proliferative diabetic retinopathy. Ultrasonography of abdomen and pelvis revealed no significant abnormalities.

After admission, patient was managed symptomatically for high blood sugar level, that is, 16 mmol/L and seizure. Intravenous 1 g levetiracetam was administered, normal saline was infused at a rate of 100 mL/h and subcutaneous insulin under basal bolus regimen insulin was administered. Furthermore, patient was supplemented with 500 mg intravenous thiamine per day along with weekly 60,000 units of oral vitamin D. Diabetic retinopathy screening and ocular coherence tomography revealed bilateral severe proliferative diabetic retinopathy with neovascularization of the iris. Pan-retinal photocoagulation was planned for the treatment of proliferative diabetic retinopathy.

Table 1. Serum biochemical parameters at the time of admission.

| Test                  | Result | Reference range | Unit   |
|-----------------------|--------|-----------------|--------|
| Random blood glucose  | 16     | 3.8–7.8         | mmol/L |
| Urea                  | 13     | 1.6–7.0         | mmol/L |
| Creatinine            | 118    | 60–115          | μmol/L |
| Sodium                | 156    | 135–146         | mEq/L  |
| Potassium             | 3.9    | 3.5–5.2         | mEq/L  |
| Amylase               | 72     | 80              | U/L    |
| Total bilirubin       | 24     | 3–21            | μmol/L |
| Direct bilirubin      | 4      | 4               | μmol/L |
| SGPT                  | 16     | 42              | U/L    |
| SGOT                  | 67     | 37              | U/L    |
| Alkaline phosphatase  | 107    | <121            | U/L    |
| PT                    | 13     | 10–12           | sec    |
| PT control            | 13.5   | 10–12           | Sec    |
| PT INR                | 0.95   | ≤1.1            | –      |
| IPTH                  | 52.4   | 7.5–53.5        | pg/ml  |
| Phosphate             | 1.15   | 1.12–1.45       | mmol/L |
| Vitamin D             | <8     | 30–100          | ng/ml  |

SGPT: serum glutamic pyruvic transferase; SGOT: serum glutamic oxaloacetic transferase; PT: prothrombin time; PT INR: prothrombin time international normalized ratio; IPTH: intact parathyroid hormone.
hyperintensity area in central pons (Figure 1) and right crus of midbrain (Figure 2) in T2 and Flair sequences suggestive of demyelination. Correlating clinical scenario and neuroimaging findings, diagnosis of ODS with CPM was made. With supportive management, patient gradually improved to the normal state with no limb weakness or fatigue or slurring of speech, and he was discharged after 21 days of hospital stay. In 1-month follow-up, patient was fine with no deficits, and his both fasting and postprandial sugar levels were normal. However, deep tendon reflexes were brisk in all the joints and bilateral plantar had extensor response.

**Discussion**

In previous studies, chronic alcohol use and alcohol withdrawal were reported being the main cause of ODS. Recent
studies have revealed hyponatremia followed by its rapid correction to be the most common cause of ODS although any kind of electrolyte imbalance can be the cause of ODS. Liver transplant recipients are at the highest risk of developing ODS. In our patient, there was no history of chronic alcohol consumption, correction of hyponatremia and liver transplantation. In our case, a rise in serum sodium was noted from 140 to 152 while the patient was admitted in previous centre. Despite hyperglycemia, the increment in sodium could be due to less intake or supplement of free water to the patient then. Occurrence of ODS having complicated DM as its underlying cause is rare, and we could identify only 16 such cases reported in English literature till date. In a recent case report by Kusumoto et al., malnutrition and severe illness with fluctuations in osmolarity were also considered risk factors for onset of ODS which was ruled out in our case.

Demyelination involves region-specific oligodendrocytes, that is, oligodendrocytes of pons, basal ganglia, mesencephalon and deep cortical layers. The glial cells of ODS-resistant brain regions are not affected by change in osmolarity. Spectrum of clinical features varies among patients of ODS and are associated with the anatomy of the lesion. Dysphagia, dysarthria, hemiplegia or paraparesis or quadriplegia, decreased deep tendon reflexes, ataxia, altered mental status, confusional state, and behavioural changes like agitation and disorientation were noticed in the patients developing CPM in case of complicated DM. The symptoms and signs, that is, loss of consciousness, altered sensorium, abnormal body movement, mild limb weakness and increased plantar reflex were present in our patient. There was history of missed insulin therapy, high blood glucose level, hypernatremia during treatment, and MRI findings in T2 and FLAIR sequences showing hyperintensity in pons and tectum suggestive of complicated DM with CPM. This diagnosis was considered after ruling out differentials such as stroke, encephalitis, meningitis, Wernicke encephalopathy, hepatic encephalopathy, primary brain tumours, metastases, radiotherapy, chemotherapy and multiple sclerosis.

Ten out of 16 case reports have shown the hyperosmolar hyperglycemic state (HHS) as the cause of ODS. Six of these case reports have described that the ODS was caused by rapid correction of serum glucose from hyperglycemic state to normal or hypoglycemic state. Three of these case reports have stated that the ODS was accompanied by HHS prior to when the patients visited hospitals. Ramineni et al. reported ODS in de novo type 2 DM with HHS on presentation suggesting its association even without sodium imbalance and its correction. Jalalzadeh et al. has reported prior history of several hypoglycemic and hyperglycemic states and indicated the fluctuations in serum osmolarity due to corresponding fluctuation in serum glucose concentration as the cause of ODS. Hegazi and Mashankar have indicated severe prolonged hyperosmolality secondary to HHS as the cause of ODS. In our case, hyponatremia developing only after the onset of symptoms and later during treatment indicates hyperglycaemia rather than hypernatremia as the cause of ODS.

In the remaining 68–13 out of 16 case reports, complicated DM without HHS and any other risk factor of ODS was the underlying cause of ODS. The case of Sharma et al. had already presented with clinical features of ODS while visiting hospital. Gourine et al. hypothesized either rapid increase of glucose after stopping insulin therapy or rapid correction of glucose as the cause of ODS. Rest four cases developed clinical features of ODS during the rapid correction of serum glucose. Our case had history of noncompliance to insulin like the case of Talluri et al. In the case of Talluri et al., the noncompliance to insulin is supposed to be the cause of alteration in glycaemic status leading to ODS.

Age of patients in the 16 case reports varied from 18 months to 93 years. Although the ODS is rarely reported in children, its occurrence in 4-year-old and 18-months-old children indicates that any age group can suffer from ODS.

Proposed mechanism for development of ODS during rapid correction of sodium is that osmolytes can easily diffuse from cytoplasm to extracellular fluid during the development of hyponatremia thus compensating the decreasing osmolality of extracellular fluid, but the same osmolytes cannot diffuse back fast enough into the cytoplasm from extracellular fluid as well as cannot replicate within the cells fast enough to balance the increasing osmolarity of extracellular fluid during the correction of hyponatremia. As the hypertonicity created in extracellular fluid during correction of hyponatremia goes uncompensated, the oligodendrocytes are degenerated. This difference in diffusion of osmolytes in the two directions clarifies why ODS develops while correcting hyponatremia but contrasts with development of ODS during the correction of hyperglycaemia because in the latter, it is decreasing osmolarity, rather than increasing osmolarity, as the cause of ODS. We suggest both increasing or decreasing osmolarity can be the cause of ODS.

Furthermore, ODS has been found in autoimmune liver disease, Sjogren’s syndrome and non-Hodgkin’s lymphoma. The pathophysiology for ODS occurring in case of autoimmune diseases, that is, autoimmune hepatitis and Sjogren’s syndrome, has not been cleared but in case of non-Hodgkin lymphoma, it is supposed to be due to systemic and metabolic stress induced by non-Hodgkin lymphoma.

There is no specific therapy for ODS, and only some patients of ODS can fully recover and remyelinate within months. Treatment under recent understanding of ODS has shown 33%–50% have better prognosis with good outcome while 33%–55% of patients require some or fully dependent
can prevent ODS in case of hyponatremia correction.\textsuperscript{1} Two correction of osmolarity under appropriate correction rate cose since there is no specific treatment for ODS; however, case, were treated supportively under controlled serum glu-

...discharge.\textsuperscript{15} Patients\textsuperscript{14,21} died during the treatment, and others had sig-

**Conclusion**

Not only rapid correction of hyponatremia, but also sudden or rapid change in extracellular fluid osmolarity due to com-

**Acknowledgements**
The authors are thankful to the patient and his family for cooperation.

**Author contributions**

SKY, SK and SP collaborated in collecting the data, interviewing the patient and patient party, and preparing the manuscript. RO, RK, BPG, RR and NP managed the case and guided throughout the process of writing this article. NG and AS were involved in man-

**Declaration of conflicting interests**
The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

**Funding**
The author(s) received no financial support for the research, author-

**Ethics approval**

Our institution does not require ethical approval for reporting indi-

**Informed consent**

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

**ORCID iDs**

Sushil Kumar Yadav \(\text{https://orcid.org/0000-0003-3840-5161}\)

Rajeev Ojha \(\text{https://orcid.org/0000-0001-7680-7036}\)

Susmin Karki \(\text{https://orcid.org/0000-0002-8570-5223}\)

**References**

1. Lambeck J, Hieber M, Dreßing A, et al. Central pontine myelinosis and osmotic demyelination syndrome. Dtsch Aerzteblatt 2019; 116: 600–606.
2. Nicole C, Marnelle C, Bouchat J, et al. Osmotic demyelina-

...sion: from an oligodendrocyte to an astrocyte perspective. Int J Mol Sci 2019; 20(5): 1124.
3. Teasdale G, Maas A, Lecky F, et al. The Glasgow Coma Scale at 40 years: standing the test of time. Lancet Neurol 2014; 13(8): 844–854.
4. Vanhouette EK, Faber CG, van N€es SI, et al. Modifying the Medical Research Council grading system through Rasch analyses. Brain 2012; 135(Pt 5): 1639–1649.
5. Morard I, Gasche Y, Kneteman M, et al. Identifying risk fac-

...transplantation: a case-control study. Neurocrit Care 2014; 20(2): 287–295.
6. Kusumoto K, Koriyama N, Kojima N, et al. Central pontine myelinolysis during treatment of hyperglycemic hypersomolar syndrome: a case report. Clin Diabetes Endocrinol 2020; 6(1): 4–9.
7. Guerrero WR, Babanh€eh N and Nadeau SE. Hemiparesis, encephalopathy, and extrapontine osmotic myelinolysis in the setting of hyperosmolar hyperglycemia. J Clin Neurosci 2013;20(6): 894–896.
8. Sharma C, Kumawat BL, Panchal M, et al. Osmotic demy-

...sion syndrome in type 1 diabetes in the absence of dys-

...electrolytæmia: an overlooked complication? BMJ Case Rep 2017; 2017: bcr2016219148.
9. Shimizu Y, Kozawa J, Hayakawa T, et al. Asymptomatic pont-

...neuron disease: a 10-year prospective study. J Child Neurol 2018; 33(2): 251–254.
16. Hirosawa T and Shimizu T. Osmotic demyelination syndrome due to hyperosmolar hyperglycemia. *Cleve Clin J Med* 2018; 85(7): 511–513.
17. O’Malley G, Moran C, Draman MS, et al. Central pontine myelinolysis complicating treatment of the hyperglycaemic hyperosmolar state. *Ann Clin Biochem* 2008; 45(Pt 4): 440–443.
18. Mao S, Liu Z and Ding M. Central pontine myelinolysis in a patient with epilepsia partialis continua and hyperglycaemic hyperosmolar state. *Ann Clin Biochem* 2011; 48(Pt 1): 79–82.
19. Rodríguez-Velver KV, Soto-Garcia AJ, Zapata-Rivera MA, et al. Osmotic demyelination syndrome as the initial manifestation of a hyperosmolar hyperglycemic state. *Case Rep Neurol Med* 2014; 2014: 652523.
20. Hegazi MO and Mashankar A. Central pontine myelinolysis in the hyperosmolar hyperglycaemic state. *Med Princ Pract* 2012; 22(1): 96–99.
21. Jalalzadeh M, Chaudhari A and Baumstein D. Prolonged altered mental status in a diabetic hemodialysis patient. *Cureus* 2021; 13(2): e13132.
22. Singh TD, Fugate JE and Rabinstein AA. Central pontine and extrapontine myelinolysis: a systematic review. *Eur J Neurol* 2014; 21(12): 1443–1450.
23. Marsili L, Gallerini S, Bartalucci M, et al. Paroxysmal painful spasms associated with central pontine myelinolysis in the context of nonketotic hyperglycemia. *J Neurol Sci.* 2018; 388: 37–39.
24. Ashrafian H and Davey P. A review of the causes of central pontine myelinosis: yet another apoptotic illness. *Eur J Neurol* 2001; 8(2): 103–109.
25. Ramineni KK, Reddy KM, Prusthi BSK, et al. Pontine myelinolysis as the presenting complication of Type 2 diabetes mellitus. *Indian J Endocrinol Metab* 2018; 22(3): 434–435.
26. Talluri S, Charumathi R, Khan M, et al. Atypical presentation of central pontine myelinolysis in hyperglycemia. *Endocrinol Diabetes Metab Case Rep* 2017; 2017(September).
27. Menon B, Bedi SS and Rao GUM. Combined central and peripheral demyelination. *J Neurosci Rural Pract* 2014; 5(1): 78–80.
28. Maturu MVS, Datla AV, Selvadasan V, et al. Rare case of central pontine myelinolysis: etiological dilemma. *Cureus* 2021; 13(11): e19644.
29. García-Grimshaw M, Jiménez-Ruiz A, Ruiz-Sandoval JL, et al. Osmotic demyelination syndrome in patients with non-Hodgkin lymphoma: a case report and literature review. *Int J Neurosci.* Epub ahead of print 24 September 2021. DOI: 10.1080/00207454.2021.1909009.