

Osmotic Demyelination Syndrome Occurs Early in The Course of Hyperosmolar Hyperglycemic State.

Jacob Raja A.S.¹, Neilasakou Linyu¹, Bhupen Rabi Das¹, Kamalom Mossang¹,
Salam Ranabir Singh², Lallan Prasad³, Santa Naorem³.

¹Post Graduate Trainee, ²Assistant Professor,

³Professor. Department of Medicine, Regional Institute of Medical Sciences, Imphal, India.

Abstract: Osmotic demyelination syndrome (ODS) is a life-threatening demyelinating syndrome. The association of ODS with hyperosmolar hyperglycaemic state (HHS) has been seldom reported. The aim of this study was to show that Osmotic Demyelination Syndrome occurs early in the course of Hyperosmolar Hyperglycaemic state and the pathophysiological mechanisms involved in ODS secondary to HHS. A 45 year old female with poorly controlled Type2 Diabetes Mellitus came to the emergency room due to loss of consciousness. She had a Glasgow Coma Scale of 3/15 and muscle power was 0/5 in all the limbs and plantar were flexor bilaterally. Blood Glucose levels were 600mg%. Plasma and urinary ketones were negative. Arterial Blood Gas analysis showed pH 7.31. HbA1C was 14.1%, Serum Calcium 7.9 mg/dL. Serum creatinine was 4.5 mg/dL. NCCT Brain came to be Normal at the time of admission. Supportive therapy was started subsequently and she was put on Insulin infusion and blood glucose was closely monitored. She regained consciousness but she was disoriented and had irrelevant talks. Muscle power came normal. One week after admission MRI Brain was taken which showed focal areas of T2 Hypersensitivities in pons and subcortical white matter of bilateral parietal lobes suggestive of osmotic demyelination syndrome. In conclusion, the association of ODS with HHS is extremely rare. The exact mechanism by which HHS produces ODS still needs to be elucidated, but we favor a rapid hypertonic insult as the most probable mechanism.

I. Background

Osmotic demyelination syndrome (ODS) is a life-threatening demyelinating syndrome, which usually occurs in the setting of a rapid correction of severe chronic hyponatremia^{1,2}. ODS is a clinical syndrome characterized by altered mental status, quadriparesis, dyspnoea, dysarthria, and dysphagia which all occur characteristically five to seven days after the correction of serum sodium³. The pathogenesis is still to be clearly understood, it is known that rapidly increasing serum osmolality shifts water out of the cells as a response to correct solute imbalance resulting in shrinkage of glial cells that can consequently lead to disruption of the blood-brain barrier allowing inflammatory mediators to enter the central nervous system damaging oligodendrocytes and myelin⁴⁻⁷.

Even though ODS has been classically thought to be exclusively secondary to a rapid correction of hyponatremia, it has also been described, even though rarely, in various other situations such as malnutrition, liver transplantation, alcoholism, hypokalemia, hypophosphatemia, AIDS, lithium toxicity, hypoglycemia, and folate deficiency, among others⁸⁻¹⁵. In all cases a growing body of evidence demonstrates that more than sodium per se, the key factor, in ODS pathogenesis, is a rapid change in serum osmoles. The association of ODS with hyperosmolar hyperglycemic state (HHS) has been seldom reported with less than five cases in the literature¹⁶⁻²⁰. Previous cases have been in the clinical scenario of concomitant hypernatremia, chronic hyperglycemia/epilepsy, and after HHS treatment.

Herein we present the case of a patient with HHS who presented with ODS early in the course of her illness. A review of previous cases and pathophysiological mechanisms involved in ODS secondary to HHS will be presented and discussed.

Case Presentation

A 45 year old female with poorly controlled Type2 Diabetes Mellitus came to the emergency room due to loss of consciousness. She was a known case of Type2 Diabetes Mellitus on Tab. Glipizide 5mg and Metformin 500mg for 10 years and long acting Isophane Insulin(30:70) for 5 years and she was a known Hypertensive on Tab Amlodipine 5mg for 5 years. She had irregular Medication.

On Physical examination, her BP was 100/60 mmHg. Heart rate was 140/min and SpO₂ was 90% in Room air. Her BMI was 27.2. Mucus membranes were dry. ECG showed Right Axis Deviation. She had a Glasgow Coma Scale of 3/15 and muscle power was 0/5 in all the limbs and plantars were flexor B/L. There was no neck rigidity. Blood Glucose levels were 600mg%. Plasma and urinary ketones were negative. ABG analysis showed pH 7.31. HbA1C was 14.1%, Serum Calcium 7.9mg/dL. Serum creatinine was 4.5mg/dL. Her eGFR

was calculated to be 22.5mL/min/1.73m². NCCT Brain came to be Normal at the time of admission. Fundus study showed Moderate NPDR. Sodium, Potassium, Phosphorous, Magnesium, Hemoglobin, WBC and Platelets were all within normal limits. Serum Albumin was 2.5mg/dl, SGOT 85 IU, SGPT 42 IU, Alkaline Phosphatase 316 IU and Total Bilirubin 0.3mg %.

Supportive therapy was started subsequently and she was hydrated with normal saline, was put on Insulin infusion and blood glucose was closely monitored.. She regained consciousness but she was disoriented and had irrelevant talks. Muscle power came normal in 3 days. Blood sugar was poorly controlled. One week after admission MRI Brain was done which showed focal areas of T2 hypersensitivities in pons and subcortical white matter of bilateral parietal lobes suggestive of osmotic demyelination syndrome. During all her admission serum sodium was documented to be within normal range. ODS was diagnosed. Serum creatinine improved slowly

Table 1: Laboratory measures during hospitalization.

Day	2	5	7	9	11		Normal range
Glucose	368	346	294	289	256		70–100 mg/dL
Sodium	148	156	150	151	149		135–145 mmol/L
Potassium	3.5	3.7	3.5	3.8	4.3		3.5–5 mmol/L
Chlorine	118	114	106	107	106		101–111 mmol/L
Creatinine	4.5	3.0	2.4	2.0	1.7		0.6–1.4 mg/dL



MRI Brain showing focal areas of T2 hypersensitivities in pons and subcortical white matter of bilateral parietal lobes suggestive of osmotic demyelination syndrome.

II. Discussion

Osmotic demyelination was first described by Adams et al. in 1959 in a series of four cases that presented paresis, pseudobulbar paralysis, and the distinctive myelin loss in the pons, attributed to alcoholism or malnutrition²². It was not until the mid-1970s that routine electrolyte tests started to be measured, that the link between chronic hyponatremia and its rapid correction was made. Since then it is not infrequent that many clinicians associate rapid correction of hyponatremia as the sole cause of ODS. Nevertheless, it is now well known that a variety of other medical conditions (where an osmotic shift has not been identified) such as alcoholism, malnutrition, cirrhosis, liver transplantation, hypokalemia, hypophosphatemia, and hypomagnesaemia, AIDS, folate deficiency, psychogenic polydipsia, beer potomania, refeeding syndrome, dialysis disequilibrium syndrome, hyperemesis gravidarum, sepsis, malignancy, lithium toxicity, prolonged diuretic use, and hypoglycemia have also been associated with ODS⁶⁻¹².

The association of ODS secondary to HHS has been seldom reported. In 1989, McComb et al. reported the first case of a ODS related to a HHS. Since admission, the patient presented with hypernatremia (169 mEq/L) and despite prompt and aggressive treatment serum sodium continued increasing (188 mEq/L). After three weeks the patient died and diagnosis of ODS was based on autopsy findings¹⁶. In 2008, O'Malley et al. reported a case of a 49-year-old woman with no previous history of type 2 diabetes that presented with glucose of 1910 mg/dL. The patient had a rapid drop of over 900 mg/dL in less than 6 hours and serum sodium

at that same time went from 134 mmol/L to 159 mmol/L. Later on, the patient developed pneumonia, sepsis, and multiorgan failure and 9 days after admission presented a flaccid quadriplegia, pseudobulbar palsy, dysarthria, and impaired swallowing. An MRI confirmed the diagnosis and the patient was discharged from hospital 90 days after admission with almost complete recovery¹⁷. Later on Burns et al. described the case of a 93-year-old man who had an initial glucose of 524 mg/dL and a serum osmolality of 317 mOsm/kg. Neurological examination and serum sodium were normal. Hyperglycemia and osmolality were corrected within 24 hours and 2 days after presentation he developed marked gait ataxia and mild dysarthria. MRI confirmed the diagnosis of ODS and at 1-month follow-up showed marked improvement in his gait unsteadiness¹⁸. More recently, Mao et al. reported the case of a 55-year-old man who had a history of multiple focal seizures 3 weeks before hospitalization. On admission he presented with focal continuous seizures, fever, right-sided hemiplegia, and absent tendon reflexes. Glucose was 685 mg/dL and serum osmolality was 318 mOsm/L. Serum sodium was within normal range and on 8 hours after HHS treatment the seizures ceased. Two days later the patient regained consciousness, muscle strength improved, and he was discharged without any neurological manifestations¹⁹. Finally, in 2013, Guerrero et al. described the case of a 23-year-old man that developed ODS days after the treatment of HHS. Surprisingly, no sodium values, serum osmolality, or outcome was mentioned in the manuscript²⁰. As described above, in four of the previous cases ODS occurred after the treatment and correction of HHS and, in the other, the patient had almost a month with seizures before developing HHS. In our case, characteristic symptoms related to ODS, confirmed by typical MRI images, were the initial manifestation of an HHS that likely developed acutely. Alternative diagnoses were ruled out, serum sodium levels were documented to be within normal range during all hospitalization, and, after the HHS resolved and supportive therapy was initiated, neurological symptoms progressively disappeared.

Although the pathogenesis of ODS is not clearly understood it is known that rapidly increasing serum osmolality shifts water out of the cells as a response to correct solute imbalance. This serves as a protective mechanism from swelling during chronic conditions of hypoosmolality that usually takes two days to be completed. In the absence of hyponatremia ODS is proposed to occur as a result of a relatively hypertonic insult in which ODS can result if the serum or the extracellular space becomes hypertonic faster than the rate at which the brain cells can compensate^{3-5,23,24}. This consequently leads to disruption of the blood-brain barrier allowing inflammatory mediators to enter the central nervous system and damage oligodendrocytes, which may further release myelin toxin and produce vasogenic edema in the central pons²⁵. Nevertheless, the breakdown concept of the blood-brain barrier as a result of osmotic stress has also been subject to debate. It has been postulated that osmotic injury may result in the release of nitric oxide or other agents harmful to tight junctions. In addition to osmotic injury and edema, the oligodendrocytes may be damaged by toxins released by injury of endothelial cells²⁶. In our case we favor the hypothesis that the hypertonic insult was the cause of ODS. It is likely that the HHS developed fast enough (during the previous day to admission) that oligodendrocytes were not able to adapt. The possibility that ODS was secondary to our treatment is plausible and cannot be excluded. However, it seems unlikely because the patient since his arrival had clinical characteristics that were compatible with ODS. Furthermore the treatment plans resulted in improvement and ultimately in full-recovery.

The clinical manifestations of ODS may vary considerably depending on the degree of pontine involvement and the presence of extrapontine lesions; paraparesis, quadriplegia, dystonia, dysphagia, ataxia, tremor, catatonia, encephalopathy, locked-in syndrome, delirium, seizures, and coma have been described. Neuropsychological findings such as attention, memory, and decision-making disturbance and even psychotic symptoms are rare but have been associated with ODS. These clinical manifestations usually occur five to seven days after the hypertonic insult but had also been described to appear after two or more weeks²⁷. It is important to remember that even though diagnoses of ODS can be made in the setting of rapid hyponatremia correction or a hypertonic insult in conjunction with characteristic clinical and radiological findings, alternate diagnoses have to be ruled out. The differential diagnosis for ODS would include stroke, primary brain tumors, metastases, encephalitis, meningitis, radiotherapy, chemotherapy, Wernicke encephalopathy, hepatic encephalopathy, and other demyelinating conditions such as multiple sclerosis²⁴. In our case, all of these conditions were excluded.

There is no specific treatment for non sodium dependent ODS rather than to treat the underlying illness and to initiate supportive measures. Nevertheless, it is important to follow the same concept, as with sodium, that whatever the hypertonic insult is it must be lowered carefully and gradually^{1,3,28}. Treatment with steroid bolus, intravenous immunoglobulin, intravenous thyrotropin-releasing hormone, or plasma exchange had also been used in some ODS cases but additional studies are warranted before their implementation in clinical practice²⁸⁻³¹. Although ODS has been previously thought as a devastating condition, recent literature shows that over 50% of the patients recover either completely or with minimal disability³². Thus, prompt diagnosis and appropriate supportive measures are mandatory.

III. Conclusion

In conclusion, the association of ODS with HHS has been seldom reported. We have described the case of a ODS with the characteristic clinical and radiological findings as the initial manifestation of HHS. The exact mechanism by which HHS produces ODS still needs to be elucidated but we favor a rapid hypertonic insult as the most plausible mechanism.

References

- [1]. M. L. Moritz and J. C. Ayus, "The pathophysiology and treatment of hyponatraemic encephalopathy: an update," *Nephrology Dialysis Transplantation*, vol. 18, no. 12, pp. 2486–2491, 2003. View at Publisher · View at Google Scholar · View at Scopus
- [2]. B. I. Karp and R. Laureno, "Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia," *Medicine*, vol. 72, no. 6, pp. 359–373, 1993. View at Google Scholar · View at Scopus
- [3]. J. M. S. Pearce, "Central pontine myelinolysis," *European Neurology*, vol. 61, no. 1, pp. 59–62, 2008. View at Publisher · View at Google Scholar · View at Scopus
- [4]. R. H. Sterns and S. M. Silver, "Brain volume regulation in response to hypo-osmolality and its correction," *The American Journal of Medicine*, vol. 119, no. 7, supplement 1, pp. S12–S16, 2006. View at Publisher · View at Google Scholar · View at Scopus
- [5]. W. D. Brown, "Osmotic demyelination disorders: central pontine and extrapontine myelinolysis," *Current Opinion in Neurology*, vol. 13, no. 6, pp. 691–697, 2000. View at Publisher · View at Google Scholar · View at Scopus
- [6]. F. G. Kengne, C. Nicaise, A. Soupart et al., "Astrocytes are an early target in osmotic demyelination syndrome," *Journal of the American Society of Nephrology*, vol. 22, no. 10, pp. 1834–1845, 2011. View at Publisher · View at Google Scholar · View at Scopus
- [7]. S. Love, "Demyelinating diseases," *Journal of Clinical Pathology*, vol. 59, no. 11, pp. 1151–1159, 2006. View at Publisher · View at Google Scholar · View at Scopus
- [8]. N. Singh, V. L. Yu, and T. Gayowski, "Central nervous system lesions in adult liver transplant recipients: clinical review with implications for management," *Medicine*, vol. 73, no. 2, pp. 110–118, 1994. View at Publisher · View at Google Scholar · View at Scopus
- [9]. W.-Y. Huang, W.-C. Weng, T.-I. Peng, L.-S. Ro, C.-W. Yang, and K.-H. Chen, "Central pontine and extrapontine myelinolysis after rapid correction of hyponatremia by hemodialysis in a uremic patient," *Renal Failure*, vol. 29, no. 5, pp. 635–638, 2007. View at Publisher · View at Google Scholar · View at Scopus
- [10]. J. W. Lohr, "Osmotic demyelination syndrome following correction of hyponatremia: association with hypokalemia," *The American Journal of Medicine*, vol. 96, no. 5, pp. 408–413, 1994. View at Publisher · View at Google Scholar · View at Scopus
- [11]. J. J. Madey, J. A. Hannah, and C. Lazaridis, "Central pontine myelinolysis following acute hypoglycemia," *Clinical Neurology and Neurosurgery*, vol. 115, no. 10, pp. 2299–2300, 2013. View at Publisher · View at Google Scholar · View at Scopus
- [12]. N. Bando, K. Watanabe, M. Tomotake, T. Taniguchi, and T. Ohmori, "Central pontine myelinolysis associated with a hypoglycemic coma in anorexia nervosa," *General Hospital Psychiatry*, vol. 27, no. 5, pp. 372–374, 2005. View at Publisher · View at Google Scholar · View at Scopus
- [13]. B. E. Tomlinson, A. M. Pierides, and W. G. Bradley, "Central pontine myelinolysis: two cases with associated electrolyte disturbance," *Quarterly Journal of Medicine*, vol. 45, no. 179, pp. 373–386, 1976. View at Google Scholar · View at Scopus
- [14]. S. R. Sanghvi, P. S. Kellerman, and L. Nanovic, "Beer potomania: an unusual cause of hyponatremia at high risk of complications from rapid correction," *American Journal of Kidney Diseases*, vol. 50, no. 4, pp. 673–680, 2007. View at Publisher · View at Google Scholar · View at Scopus
- [15]. B. Mozes, A. Pines, D. Werner, D. Olchovsky, P. Lieberman, and O. Frankl, "Thiazide-induced hyponatremia: An unusual neurologic course," *Southern Medical Journal*, vol. 79, no. 5, pp. 629–631, 1986. View at Publisher · View at Google Scholar · View at Scopus
- [16]. R. D. McComb, R. F. Pfeiffer, J. H. Casey, G. Wolcott, and D. J. Till, "Lateral pontine and extrapontine myelinolysis associated with hypernatremia and hyperglycemia," *Clinical Neuropathology*, vol. 8, no. 6, pp. 284–288, 1989. View at Google Scholar · View at Scopus
- [17]. G. O'Malley, C. Moran, M. S. Draman, T. King, D. Smith, and A. Agha, "Central pontine myelinolysis complicating treatment of the hyperglycaemic hyperosmolar state," *Annals of Clinical Biochemistry*, vol. 45, no. 4, pp. 440–443, 2008. View at Publisher · View at Google Scholar · View at Scopus
- [18]. J. D. Burns, S. C. Kosa, and E. F. M. Wijdicks, "Central pontine myelinolysis in a patient with hyperosmolar hyperglycemia and consistently normal serum sodium," *Neurocritical Care*, vol. 11, no. 2, pp. 251–254, 2009. View at Publisher · View at Google Scholar · View at Scopus
- [19]. S. Mao, Z. Liu, and M. Ding, "Central pontine myelinolysis in a patient with epilepsia partialis continua and hyperglycaemic hyperosmolar state," *Annals of Clinical Biochemistry*, vol. 48, no. 1, pp. 79–82, 2011. View at Publisher · View at Google Scholar · View at Scopus
- [20]. W. R. Guerrero, H. Dababneh, and S. E. Nadeau, "Hemiparesis, encephalopathy, and extrapontine osmotic myelinolysis in the setting of hyperosmolar hyperglycemia," *Journal of Clinical Neuroscience*, vol. 20, no. 6, pp. 894–896, 2013. View at Publisher · View at Google Scholar · View at Scopus
- [21]. A. E. Kitabchi, G. E. Umpierrez, J. M. Miles, and J. N. Fisher, "Hyperglycemic crises in adult patients with diabetes," *Diabetes Care*, vol. 32, no. 7, pp. 1335–1343, 2009. View at Publisher · View at Google Scholar · View at Scopus
- [22]. R. D. Adams, M. Victor, and E. L. Mancall, "Central pontine myelinolysis: a hitherto undescribed disease occurring in alcoholic and malnourished patients," *Archives of Neurology & Psychiatry*, vol. 81, no. 2, pp. 154–172, 1959. View at Publisher · View at Google Scholar · View at Scopus
- [23]. B. K. Kleinschmidt-Demasters, A. M. Rojiani, and C. M. Filley, "Central and extrapontine myelinolysis : then and now," *Journal of Neuropathology and Experimental Neurology*, vol. 65, no. 1, pp. 1–11, 2006. View at Publisher · View at Google Scholar · View at Scopus
- [24]. H. Ashrafian and P. Davey, "A review of the causes of central pontine myelinolysis: yet another apoptotic illness?" *European Journal of Neurology*, vol. 8, no. 2, pp. 103–109, 2001. View at Publisher · View at Google Scholar · View at Scopus
- [25]. J. C. Ayus, S. G. Achinger, and A. Arieff, "Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia," *American Journal of Physiology - Renal Physiology*, vol. 295, no. 3, pp. F619–F624, 2008. View at Publisher · View at Google Scholar · View at Scopus
- [26]. A. M. Alleman, "Osmotic demyelination syndrome: central pontine myelinolysis and extrapontine myelinolysis," *Seminars in Ultrasound, CT and MRI*, vol. 35, no. 2, pp. 153–159, 2014. View at Publisher · View at Google Scholar · View at Scopus

- [27]. M. Walterfang, A. Goh, R. Mocellin, A. Evans, and D. Velakoulis, "Peduncular hallucinosis secondary to central pontine myelinolysis," *Psychiatry and Clinical Neurosciences*, vol. 66, no. 7, pp. 618–621, 2012. [View at Publisher](#) · [View at Google Scholar](#) · [View at Scopus](#)
- [28]. R. J. Martin, "Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes," *Neurology in Practice*, vol. 75, no. 3, pp. iii22–iii28, 2004. [View at Publisher](#) · [View at Google Scholar](#) · [View at Scopus](#)
- [29]. D. Bibl, C. Lampl, C. Gabriel, G. Jüngling, H. Brock, and G. Köstler, "Treatment of central pontine myelinolysis with therapeutic plasmapheresis," *The Lancet*, vol. 353, no. 9159, p. 1155, 1999. [View at Google Scholar](#) · [View at Scopus](#)
- [30]. F. H. Saner, S. Koeppen, M. Meyer et al., "Treatment of central pontine myelinolysis with plasmapheresis and immunoglobulins in liver transplant patient," *Transplant International*, vol. 21, no. 4, pp. 390–391, 2008. [View at Publisher](#) · [View at Google Scholar](#) · [View at Scopus](#)
- [31]. É. F. Zein, S. E. Karaa, F. Rollet, P. Blanche, and R. E. Chemaly, "Treatment of central pontine myelinolysis with thyrotropin-releasing hormone," *Presse Medicale*, vol. 35, no. 4, pp. 618–620, 2006. [View at Publisher](#) · [View at Google Scholar](#) · [View at Scopus](#)
- [32]. H. Menger and J. Jörg, "Outcome of central pontine and extrapontine myelinolysis (n=44)," *Journal of Neurology*, vol. 246, no. 8, pp. 700–705, 1999. [View at Publisher](#) · [View at Google Scholar](#) · [View at Scopus](#)