ORIGINAL RESEARCH PAPER

Neurology

KEY WORDS: osmotic demyelination syndrome, hyperglycemia, central pontine myelinolysis

OSMOTIC DEMYELINATION SYNDROME IN UNUSUAL SETTINGS

Sakthi Velayutham S*	Senior Assistant professor of Neurology, Stanley Medical college, Chennai *Corresponding Author
Sowmini PR	Senior Assistant professor of Neurology, Stanley Medical college, Chennai
Malcolm Jeyaraj K	Senior Assistant professor of Neurology, Stanley Medical college, Chennai
Sathish Kumar M	Assistant professor of Neurology, Stanley Medical college, Chennai
Arunan S	Professor of Neurology, Stanley Medical college, Chennai

ABSTRACT

Objective: To highlight the occurrence of osmotic demyelination syndrome (ODS) in settings other than the classical ODS induced by rapid correction of hyponatremic states. The background, clinico- radiological features, treatment and outcome of eight ODS patients are discussed here. **Materials and Methods:** We encountered eight patients with ODS in uncommon clinical settings at the department of neurology, Government Stanley medical college hospital, Chennai between April 2017 to October 2018. Patients were evaluated, investigated, treated and outcome was assessed. **Results:** Eight patients in the age group 22 to 60 years had ODS. The clinical presentations were diverse. Akinetic mutism was the commonest presenting feature of ODS. Four out of eight patients had hyperglycemia out of which three had diabetic ketoacidosis (DKA) and one was in hyperglycemic hyperosmolar state (HHS). Two patients with chronic kidney disease (CKD) developed myelinolysis following hemodialysis. One patient each in post liver transplant state and following alcohol binge were diagnosed with ODS. Serum sodium levels were in normal range and there was no undue fluctuation in all. Four had central pontine myelinolysis (CPM), three had Extrapontine myelinolysis (EPM) and one had both in Magnetic Resonance Imaging (MRI) of Brain. Background illnesses were addressed. Five patients were independent with mRS of 1 and one patient had mRS of 2 at the end of 3 months and two CKD patients succumbed due to disease per se. **Conclusion:** ODS commonly occurs in the setting of rapid correction of hyponatremia especially in chronic alcoholics and debilitated individuals. We have described myelinolysis in diabetic ketoacidosis, hyperglycemic hyperosmolar state, Renal failure following dialysis, post liver transplant and alcohol binge drinking where there were no undue fluctuation in sodium levels. The prognosis is variable and also depends on presence of secondary complications like deep venous thrombosis, sepsis and aspiration pneumonitis.

INTRODUCTION:

Osmotic demyelination syndrome (ODS) comprises central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) [1]. In 1959 Adams and colleagues described CPM in chronic alcoholics and malnourished [2]. In 1962 EPM was also described recognizing that myelinolysis can occur at sites other than pons [3]. Focal and symmetric myelin loss occurs after aggressive correction of hypo or hyperosmolar state [4]. Myelinolysis differs from that of demyelination in that there is no inflammatory infiltrate in the former [3]. The classical setting for CPM and EPM is rapid correction of chronic hyponatremia in a chronic alcoholic or debilitated and malnourished individual [2]. ODS can also occur in various unusual clinical settings where there is large osmolality shifts like hyperglycemia[5], renal failure [13], burns [3], alcohol binge drinking [3], liver transplant [7], severe hypophosphatemia [3] , hypokalemia [3]. In this case series we describe ODS in uncommon scenarios we encountered in our hospital where there were normonatremia throughout the clinical course.

MATERIALS and METHODS:

This study was conducted between April 2017 to October 2018 at Department of Neurology, Government Stanley Medical college, Chennai. We included 8 patients who had radiological features of ODS (based on MRI sequences T2,FLAIR and DWI) without undue fluctuations in the sodium levels. The clinical features, etiology, clinical course and outcome were described for each patient.

Case 1:

A 61 year old female admitted with acute onset of unsteadiness while walking, slurred speech and emotional lability for a week. She was a diabetic for the past 7 years with poor glycemic control. Her random blood sugar was 602 mg/dl at the time of admission. On examination she was lethargic, horizontal gaze palsy, spastic dysarthria, gait and appendicular ataxia & pseudobulbar affect were noted. Her glycemic profile were Fasting Blood Sugar of 403 mg/dl, Postprandial Blood Sugar of 527 mg/dl, HbA1c of 11.5 % and urine ketones were negative. Serum sodium on admission was 134 meq and repeat values were also within normal limits. Other biochemical investigations like Renal function and other electrolytes were within normal limits. MRI brain revealed CPM and EPM lesions in bilateral thalamus and basal ganglia (fig 1). Patient was hydrated well and insulin was optimised to maintain euglycemia. Patient had marked improvement in gait and horizontal gaze palsy . Residual mild appendicular ataxia (bilateral) and dysarthria was present at the time of discharge.

Case 2 :

A 45 year old male diabetic for 10 years was admitted with fever, lethargy , cough with expectoration for the past 3 days. Initally he was dehydrated, drowsy , localising painful stimuli, opened eyes to pain stimuli and groaning. His fasting and post prandial blood sugars were 355 mg/dl and 496 mg/dl respectively with ketone positivity in urine. Total leucocyte count (18,400 cells /cu.mm) was elevated with neutrophilia at the time of admission with normal sodium level (133 meq/l).

He was hydrated well and antibiotics , bronchodilators and insulin administered . Patient became alert, fever subsided after a week of treatment but he developed new symptoms in the form of unsteadiness while walking and dysarthria. This time examination revealed gait and appendicular ataxia and spastic dysarthria. MRI brain revealed CPM lesions only and repeat sodium values were normal. Patient showed

spontaneous recovery after 10 days with residual symptoms of mild appendicular ataxia bilaterally.

Case 3 :
We experienced similar situation in another 45 year old female where she had high blood sugars with urine ketones positivity. She had Both CPM and EPM in basal ganglia . Additionally she had symptomatic parkinsonism and responded well to levodopa/carbidopa.

Case 4:
Another 50 yr old male with high blood sugars (RBS 547 mg/dl) with urine ketones negativity admitted with spastic dysarthria and gait ataxia and pseudobulbar affect who subsequently improved well without residual deficits after a week. He had only CPM lesions

Case 5 :
A 27 year old male developed acute onset of difficulty in swallowing and nasal regurgitation and dysarthria for 3 days following a binge drinking alcohol for a week. Patient was conscious oriented, gag reflex was exaggerated, spastic dysarthria and no motor weakness. Bilateral appendicular incoordination was noted. Basic biochemistry was normal and electrolytes normal. MRI revealed CPM lesions only (fig 2). Supportive treatment given and by 5 th day patient was able to swallow (ryles tube removed) and could speak better

Case 6 :
A 45 year old male who underwent liver transplant became stuporous on Post Operative Day 3. On examination (initially) he was stuporous with intact brainstem reflexes .He couldn't move his limbs but winced to deep pain. Pt MRI revealed CPM and EPM lesions including bilateral frontal subcortical lesions with diffusion restriction (fig 3 and fig 4). On subsequent days patient evolved into an akinetic mute state. His eyes were spontaneously open but unable to communicate or move his limbs. Amantadine was started initially 200 mg/d later 300 mg/d to improve the abulic state beside immunosuppressive medications and supportive treatment . After 2 months he started to move his limbs , could speak but with slurring and was able to walk with support

Case 7 :
A 27 year old male brought to casualty with c/o breathlessness and anasarca for 3 days. He was diagnosed to have acute on chronic kidney disease (CKD) and underwent hemodialysis (HD) 1 cycle. The next day pt developed akinetic mute state. His biochemical investigations revealed Hb of 7g/dl, (pre HD) urea 186 mg/dl , Creatinine 7.8 mg/dl, Na + 135 meq/l , k+ 6.5 (Post HD) urea 165 mg/dl , creatinine 6.3 mg/dl, Na+ 130 meq/l , k+ 5.5 meq/l. MRI brain revealed T2 FLAIR hyperintensity in bilateral basal ganglia regions. After a week pt succumbed due to aspiration pneumonitis and sepsis.

Case 8 :
We encountered a similar situation in a 22 yr old male with CKD who after undergoing HD developed catatonia and he had EPM alone in bilateral basal ganglia regions. 2 days later he died due to his renal failure.

RESULTS:
Eight patients had ODS ranging in the age group 22 to 60 years . The clinical presentation were diverse. **Akinetic mutism** was the commonest presenting feature of ODS. Five out of eight patients had uncontrolled **hyperglycemia** out of which two had diabetic ketoacidosis (DKA) and two were in hyperglycemic hyperosmolar state (HHS). Two patients with **Chronic Kidney Disease(CKD)** developed ODS following Hemodialysis (HD). One patient developed ODS following **liver transplant** and another after **binge drinking** of alcohol. Serum sodium levels were in normal range and there were no undue fluctuation in all the patients. **Four had CPM, three had EPM and one had both in MRI Brain**. Background illness was addressed and supportive treatment provided for all. Six had near normal recovery at the end of 3 months and two CKD patients expired within a week of diagnosis of ODS

DISCUSSION:
ODS is a rare entity and overall incidence in critical care unit settings from our part of the country is 2.5% out of which pontine lesions constitute 41% whereas pontine and extrapontine lesions constitute 23% of ODS [27]. CPM and EPM though classically occurs during rapid correction of hyponatremia in a chronic alcoholic or a debilated individual has been described in various clinical situations where there might be large osmolality shifts [4]. Our study helps to confirm the associations of not so common scenarios like Hyperglycemia, uremia, alcohol binge intake, post liver transplant with ODS. The pathophysiology of CPM is linked to sudden cell shrinkage particularly oligodendrocytes (responsible for central nervous system myelination) following rapid increase in serum osmolality due to rapid correction of hyponatremia. Oligodendrocytes undergo apoptosis following the hypertonic insult resulting in myelinolysis [3]. In hyperglycemia it is the relative hypertonicity that plays a major role in the pathogenesis of ODS. Our patients with hyperglycemia had high blood sugar values substantial to cause a rise in osmolality outpacing the ability of the oligodendrocytes to adapt to the changing osmolality by accumulating idiogenic osmoles [5]. Joseph D burns reported a similar case of a nonagenarian who presented with isolated gait ataxia and dysarthria secondary to hyperglycemia without fluctuations in sodium homeostasis. ODS can develop either due to hyperglycemia per se or during correction of hyperglycemia using insulin [6] .CPM following orthotopic liver transplant varies from 5 to 10 % [7,8]. ODS can occur in patients with low, high or normal sodium levels particularly in liver transplant patients [9].CPM is multifactorial in etiology partly due to glial / neuronal stress and partly to deficiency in generation of organic osmolytes [10]. In liver transplant patients there is deficiency of organic osmolytes like myo inositol making them vulnerable to CPM [11] .Also the glial cells do not have adequate glucose to meet the high metabolic demands (for Na+k+ ATPase pump) during osmolality shifts [12]. Tarhan et al reported 17 cases with renal failure and ODS who underwent hemodialysis at least once [13]. They noted that only one patient had rapid correction of hyponatremia and extrapontine sites involvement (71 %) was little higher than pontine sites (65 %). Atul abishek Jha reported a young male with End stage renal disease on hemodialysis with normonatremia who developed spastic quadriparesis with CPM lesions in MRI but subsequently improved [14]. Volumetric analysis of MRI brain after hemodialysis by Walters et al showed 3 % increase in brain volume [15]. During or after hemodialysis urea (though an osmotically ineffective solute) is suddenly reduced making plasma hypotonic and there is shift of fluid from extracellular compartment to brain cells [16] . ODS can occur either during or after hemodialysis. Both of our CKD patients developed ODS post hemodialysis. Following a binge drinking of alcohol if there is refeeding the sudden osmotic stress may not be dealt adequately by the brain which was devoid of energy and leading to apopotosis of oligodendrocytes [17] . Chronic alcoholics are deficient of thiamine which has a key role in providing energy to glial/neuronal cells [18] .

The clinical manifestations of ODS is variable. It has biphasic course with initially an encephalopathy followed by gradual improvement in sensorium only to deteroriate later manifesting as spastic quadriparesis of varying degree with dysphagia , dysarthria, ataxia and oculomotor dysfunction [1]. The involvement of bilateral pontine nuclei, corticopontocerebellar and corticobulbar fibres results in the above clinical manifestations. The extrapontine sites mainly bilateral basal ganglia involvement results in

movement disorders like parkinsonism and catatonia. Spastic quadriparesis was the commonest clinical presentation in our study though we noted symptomatic parkinsonism in a patient with hyperglycemia who responded well to dopaminergic medications. ODS is a clinicoradiological entity hence MRI plays a vital role in increasing the sensitivity of the diagnosis. Well described findings include focal symmetric, trident or mexican hat shaped, high signal in the basis pontis on T2-weighted and fluid attenuation inversion recovery (FLAIR) sequences with corresponding decreased T1-weighted signal [19] . Extrapontine lesions are most often located in the midbrain, thalami and basal ganglia [20] . Lesion location, volume, diffusion restriction and contrast enhancement (seen in 1/5th cases) do not influence prognosis [21] . Ruzek et al. demonstrated diffusion restriction within 24 hours of onset of quadriparesis as the first imaging manifestation of ODS in the setting of otherwise normal conventional MRI sequences [22] . In our study we encountered both CPM and EPM lesions where majority had restricted diffusion and liver transplant patient had both CPM and EPM lesions. About half of the patients with ODS do have a better functional recovery in contrast to the previous thought that ODS almost always carry a dismal prognosis. Low GCS, severe hyponatremia, superadded hypokalemia, low functional scores during hospital stay are all poor prognostic factors [21]. it is confirmed in our study that six out of eight patients including the liver transplant patient had significant meaningful recovery. The two CKD patients would have succumbed to the disease per se rather than ODS alone. Till date there is no specific therapy for ODS. There are individual case reports supporting the role of plasma exchange [23], immunoglobulin [24], reinduction of hyponatremia [25], thyrotropin releasing hormone and corticosteroids [26] though their benefit is not proved beyond doubt. Symptomatic and supportive treatment is only feasible at present. Mortality varies widely from 6% to 90 % as per literature evidence [28]. Menger et al reported in their study that out of 34 patients 32 survived. Of these 10 were dependent, 11 were independent but with deficits and 11 completely recovered. They concluded that if secondary complications such as aspiration pneumonia, sepsis, deep venous thrombosis can be avoided CPM patients survival rate improve [29].

CONCLUSION :

Our study helps to confirm that ODS can occur in varied settings like hyperglycemia, uremia , liver transplant and alcohol binge drinking without disturbance of sodium homeostasis. ODS should be suspected when there is a deterioration in a critically ill patient who improved initially but subsequently presenting with features of pseudobulbar palsy, locked in like state or catatonia. MRI is the best imaging modality in ODS particularly diffusion weighted sequence which is helpful in picking up early lesions. Prognosis is generally good with best supportive care.

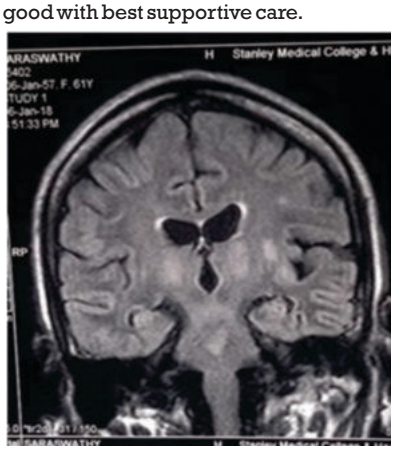

Fig 1: T2 FLAIR MRI of brain showing bilateral hyperintensity in basal ganglia , pons in a 61 year female with hyperglycemia who presented with pseudobulbar palsy and appendicular ataxia

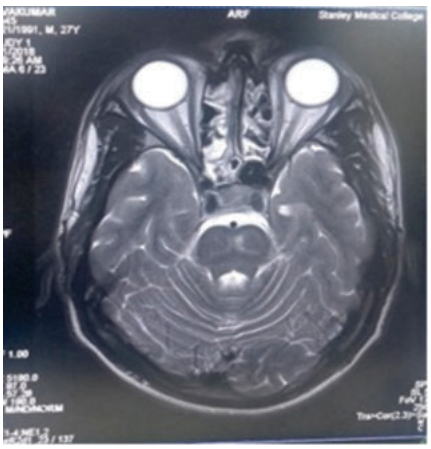

Fig 2: T2 axial MRI of brain showing hyperintensity in pons in a 27 yr old male who developed pseudobulbar palsy after binge drinking of alcohol

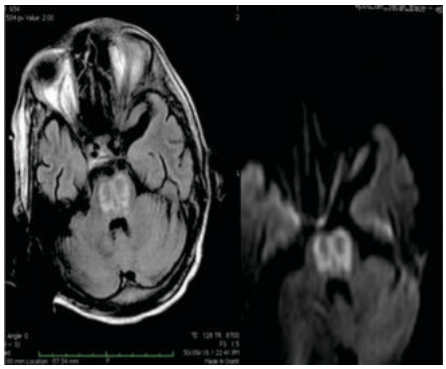

Fig 3: T2 axial FLAIR and diffusion weighted MRI showing hyperintensity in pons with diffusion restriction in a 45 year old male with post liver transplant ODS who developed locked in state

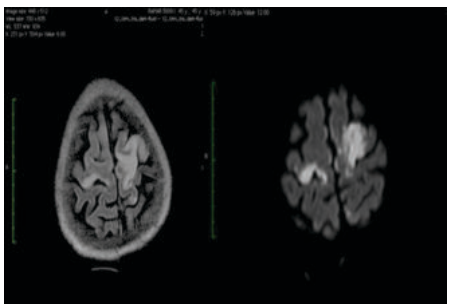

Fig 4 : T2 axial FLAIR and diffusion weighted MRI showing hyperintensity in bilateral frontal cortices with diffusion restriction in the post liver transplant patient who had cortical lesions along with pontine myelinolysis

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