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ELUCIDATION OF OSMOTIC DEMYELINATING SYNDROME DUE TO HYPONATREMIA

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Abstract:
Osmotic demyelinating syndrome is a non-inflammatory demyelinating disease that commonly involves basal region of central pons and other areas of brain including basal ganglia, thalamus, lateral geniculate bodies. It has no incidence of occurrence and which were diagnosed mostly through autopsy and magnetic resonance imaging (MRI) findings. It occurs mainly due to the chronic alcohol intake, electrolyte imbalances, drug induced hyponatremia, etc. The most common cause of osmotic demyelinating syndrome is hyponatremia in clinical settings. The pathophysiology of Osmotic demyelinating syndrome is unknown and hypothesis is the acute and chronic hyponatremia which may disrupt the astrocytes of the basal ganglia. The rapid and slow correction or excessive correction of hyponatremia leads to osmotic demyelinating syndrome. The immediate treatment is required for improving patient's health condition and better outcomes. The neurological symptoms may result as a consequence of osmotic demyelinating syndrome and supportive and nutritional therapy is required for the treatment. The article discusses about the relation between hyponatremia and osmotic demyelinating syndrome in different hospital settings through case studies.

Key words: *Osmotic demyelinating syndrome, hyponatremia, basal ganglia, sodium, electrolyte imbalances.*

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INTRODUCTION:

Osmotic demyelinating syndrome (ODS) is a non-inflammatory demyelinating disease which commonly involves the basal region of central pons and also other areas of the brain including basal ganglia, thalamus and lateral geniculate bodies. The main cause of this syndrome is alcoholism, malnourishment, electrolyte imbalances. The most common electrolyte imbalance is hyponatremia. The ODS is rarely diagnosed with an undetermined incidence in which many cases are detected through autopsy findings[1]. ODS involves both pontine and extra pontine myelinolysis with primary pathophysiology of reduced adaptive capacity of neuroglia to large changes in the serum osmolality or the edema of a cell due to the fluctuations in electrolyte forces that lead to compression and demyelination of fiber tracts [2]. The pathophysiology of ODS is unknown and yet to be elucidated. Some theories include the adaptation of the brain to severely low levels of intracellular osmolyte and frequent exposure to hypertonic stress as a result of rapid correction of hyponatremia. Due to this intracellular sodium and chloride levels increase to a higher level than normal as a result of cellular dehydration. The accurate diagnosis can be done using brain magnetic resonance imaging (MRI) scan. T1 weighted images explain the symmetric hypointense lesions and T2 weighted images explain symmetric hyperintense lesions. The characteristic 'bat-winged' or 'trident-shaped' appearance in the center of pons which is the classic finding on MRI for CPM (Central Pontine Myelinolysis). There are many therapies methods available for ODS. Despite many case series and reports including thyrotropin-releasing hormone, plasmapheresis, steroids and immunoglobulins there is a small amount of data due to lack of large-scale studies proving effectiveness along with prevention of secondary complications[1]. Alteration in sodium levels is one of the most common electrolyte imbalances from which hyponatremia is mostly observed. Hypernatremia occurs in 14-42% of the patients who are hospitalized and has a higher rate of mortality about 6-100%. Acute or severe hyponatremia leads to life-threatening cerebral edema. The clinical manifestations of ODS are encephalopathy, seizures, parkinsonian-like movement disorders and locked-in syndrome. This article discusses the relation between hyponatremia and ODS in a hospital setting through case studies[3].

EPIDEMIOLOGY

ODS is a rare condition which has no incidence of occurrence which were diagnosed mostly through autopsy. It was first described by Adams et al., as solely pontine entity which was diagnosed through an autopsy in 1987 which included 58 cases of ODS which included CPM in half, 30% of combination of CPM and EPM and isolated EPM in 20% cases. EPM symptoms were masked by pontine dysfunction so the disease cannot be diagnosed[1].

HYPONATREMIA

It is the most common electrolyte disorder occurs when the sodium level is less than 135mmol/liter. It was stated in a Dutch systematic review of 53 studies that prevalence of mild hyponatremia in geriatric hospital wards are 22.2%, in non- geriatric wards it was 6.0%, in intensive care unit it was 17.2%. When the sodium levels were less than 125mmol/L and the prevalence was 4.5%, 0.8% and 10.3% respectively. The post-operative complications. Length of hospital stay and mortality of hyponatremia were mostly seen in heart failure patients who undergo cardiac surgery[8]. Raising the serum sodium level by 4-6 m Eq/L can resolve the cerebral edema but rapid correction of severe hyponatremia can lead to mortality in hospital setting from 6% to 10%. The rapid correction leads to ODS and CPM[3].

ETIOLOGY AND PATHOPHYSIOLOGY OF HYPONATREMIA

The hyponatremia is classified based on the volume status in the body like hypovolemia, euvolemia and hypervolemia. Hypovolemia means decreased total body water content in which sodium levels are decreased, euvolemia is increased total body water with normal range of sodium level and hypervolemia is increased body water compared to sodium levels in the body. The plasma osmolality differences lead to the hyponatremia. Osmolality is defined as the total concentration of solutes in water. The solutes which do not cross the cell membrane create effective osmolality gradient. Effective osmolality is the osmotic pressure and flow of water. The regulation of antidiuretic hormone leads to maintenance of strict plasma osmolality. When the plasma osmolality increases, ADH is released and water is reabsorbed by the kidneys which in turn decreases the serum osmolality. If the serum osmolality decreases, ADH is also decreased leading to diuresis of free water and homeostasis[8].

Assumed pathophysiology of ODS:

Astrocyte chronically adapted to hyponatremia or overly rapid correction of hyponatremia

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Astrocyte apoptosis

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Disruption of blood brain barrier and exposure to inflammatory cytokines

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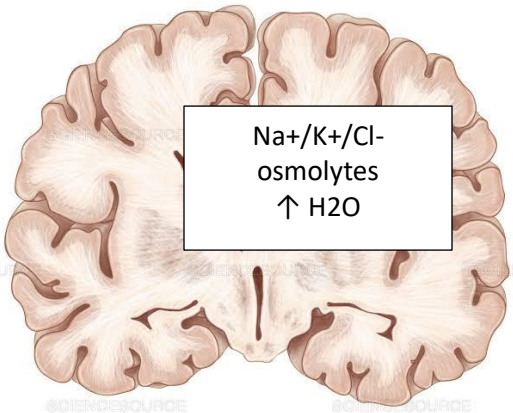
Microglial activation

↓

Osmotic demyelination



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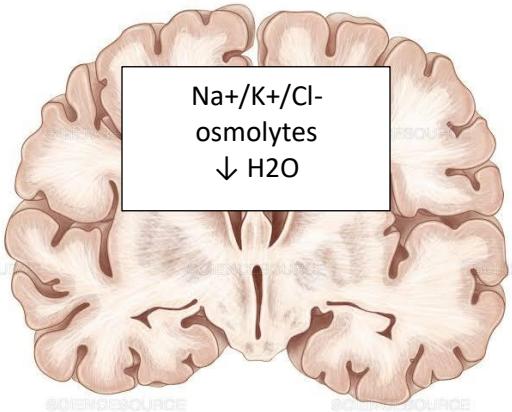

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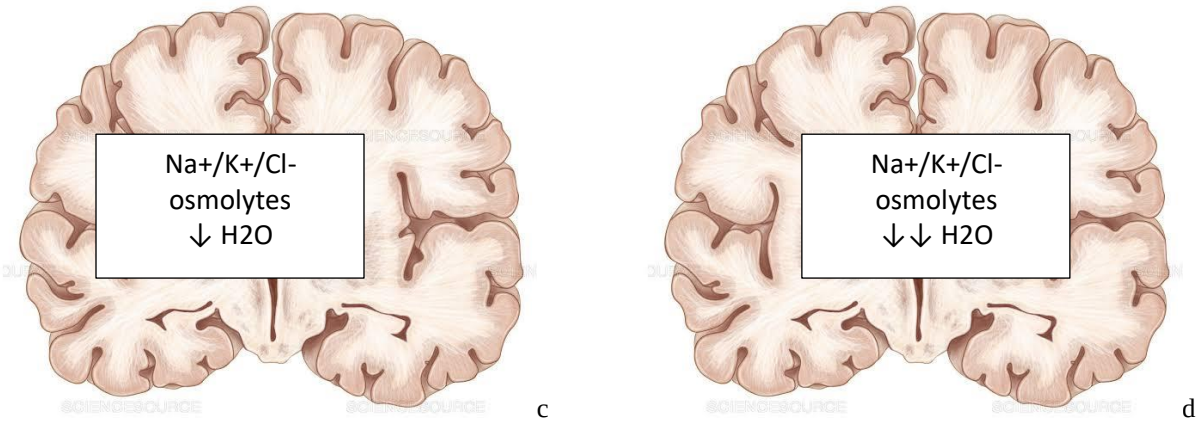

c d

a) Normonatremia where sodium and water levels are balanced.
b) Acute hyponatremia where sodium levels are decreased and water levels are increased.
c) Chronic hyponatremia where sodium levels are severely decreased and water levels are increased.
d) Osmotic demyelination, where sodium levels are normal or increased and water levels are decreased.

DIAGNOSIS AND TREATMENT OF HYPONATREMIA

The most common symptoms of hyponatremia include polydipsia, muscle cramps, headache, falls, confusion, altered mental status, obtundation, status epilepticus and coma which need an acute intervention. The volume of fluids and sodium levels should be assessed prior diagnosis of underlying cause. The diagnosis part includes history and physical examination including the priority to cardiac, pulmonary, surgical, gastrointestinal, endocrine, renal, neurologic and cancer histories. Some drugs may cause hypovolemia like diuretics, carbamazepine. And selective serotonin reuptake inhibitors. Illicit drug use and alcohol intake (especially beer) can cause hyponatremia. The tests should include urinary sodium and creatinine levels, thyroid stimulating hormone, urinary uric acid adrenocorticotropic hormone, plasma cortisol, brain natriuretic peptide is estimated. Pseudohyponatremia is estimated when low levels of sodium are actually normal. Causes can be hyperglycemia, hyperproteinemia, mannitol usage or laboratory errors. The euvolemia conditions are observed in these situations and correction of sodium calculation is required in hyperglycemia. In hypovolemic hyponatremia the signs and symptoms include volume depletion, diarrhea, tachycardia, elevated blood urea nitrogen levels. Fractional excretion of sodium is diuretic induced natriuresis, so fractional excretion of urea can be utilized in these patients. Treatment consists of volume repletion with 0.9% saline, use of salt tablets occasionally and monitoring of urine output more than 100 ml per hour is a warning sign of overcorrection of hyponatremia. Euvolemia hyponatremia is commonly caused by syndrome of inappropriate anti-diuretic hormone (SIADH), hypothyroidism and glucocorticoid deficiency. It can be diagnosed by collecting history from patient and physical examination, low serum uric acid levels, normal BUN to creatinine ratio, spot urinary sodium >20 mmol/L. Treatment include fluid restriction and treating the underlying cause. Fluid intake should be less than or equal to 500ml and less than daily urine output. In hypervolemic hyponatremia, the effective arterial blood volume is decreased compared with venous volume, resulting in increased ADH secretion. This type of hypovolemia occurs when the kidneys cannot excrete water efficiently. The causes are heart failure, cirrhosis, kidney injury. Treatment consists of sodium and fluid restriction, diuretic therapy for increasing the excretion of solute free water. Severe hypovolemic hyponatremia occurs when sodium levels fall to 120 mmol/L in less than 24 hours with severe symptoms of coma, seizures etc. Severe symptomatic hyponatremia should be corrected immediately as it leads to cerebral edema, irreversible neurologic damage, respiratory distress, brainstem herniation and death. Treatment includes 3% hypertonic saline infused at a rate of 0.5 to 2 mg per kg per hour until the symptoms resolve[8].

HOW MUCH CORRECTION OF SODIUM IS ENOUGH?

Acute hyponatremia is seen with seizures, coma and can reflect cerebral edema. Majority of the studies suggest that the rapid correction of 4-6 mmol/l is sufficient to stop hyponatremic seizures after first few hours of successful treatment. After a certain osmolality, a few milliliters can also cause additional intracranial pressure due to increased intracellular volume. In the same way, a small decrease in volume reduces the intracranial pressure. In normonatremic

patients treated for cerebral edema, raise of serum sodium levels by 5 mmol/l with hypertonic saline is sufficient to reduce the intracranial pressure. Correction rates could be affected by underlying causes like hyponatremia due to heart failure, cirrhosis, kidney injury or malignancy which does not resolve immediately and may not be treated. Patients with such type of disorders die in the hospital setting only. Drug induced hyponatremia can be reduced by withdrawing the medications and this type of patients rarely die in the hospital. Lower serum levels are more associated with the rapid correction and these types of cases have low mortality. Patients with low levels of sodium are often diagnosed with drug induced hyponatremia and mild levels of sodium in potentially fatal illness induced hyponatremia.

HOW MUCH CORRECTION OF SODIUM IS SEVERE?

Rapid correction and excessive correction of chronic hyponatremia leads to ODS although it is rare, but actually it is more common than herniation due to untreated acute hyponatremia. The Mayo clinic conducted a survey for 16 years found that there were no patients with fatal postoperative hyponatremia and 6 patients were identified with ODS. In another 11year survey, 18 patients were identified with MRI documented demyelination in one year and in 5 patients, it was found that serum sodium was less than or equal to 105 mmol/l and in one patient it was less than 110 mmol/l. MRI can detect the lesions of ODS in patients who are alive. When symptoms are detected restriction diffusion on MRI may be enough for identifying the lesions. The clinical and diagnostic findings are reversible and some patients improve after a period of neurologic disability. Autopsy or MRI defined cases report the most severe stage of injury caused by excessive correction of hyponatremia. More sensitive injury is difficult to detect. The rapid correction of hyponatremia is not only the reason for autopsy and MRI detected lesions and it may be inappropriate to correct the hyponatremia without the features of ODS[6].

ODS AFTER THE CORRECTION OF HYPONATREMIA – CASE STUDY

A case study reported a 45year old man with a history of cerebro-vascular accident (CVA) without the visual defects. The patient had presented with hypertension, hyperlipidemia to the outside hospital with one day of dizziness, fatigue, nausea and vomiting while the patient is on business trip. Nausea and vomiting began after eating at a buffet 3 days prior to his presentation to the hospital. He had been drinking a ton of water since the vomiting had begun. He is using hydrochlorothiazide, aspirin, amlodipine, benazepril. The blood pressure was 98/48 mm Hg and heart rate was 86/min, respiratory rate was 18/min and he was afebrile. After admission the laboratory values were Sodium – 101mmol/L, potassium- 2.2 mmol/L, chloride- 65mmol/L, bicarbonate- 45mmol/L and glucose- 104 mg/dL. 3% normal saline was infused with supplemental KCL was initiated. For the next 24 hours, his sodium levels were increased to 129mmol/L. The patient was discharged with 130mmol/L sodium levels. He was instructed for follow-up for early movement disorders. The patient had developed upper extremity tremor and confusion and presented 3 days later with difficulty speaking, drooling and emotional lability, shuffling gait. The findings for sodium levels was normal. MRI of brain revealed findings relevant to ODS. Methyl prednisolone and dextromethorphan-quinidine were prescribed.

In this case, the patient responded by ingesting large amounts of water that lead to hyponatremia and hypokalemia. The initial condition is hypovolemic hypotonic hyponatremia due to his thiazide use. Due to ingestion of large amounts of water he was affected with euvolemic hypotonic hyponatremia. Rapid correction of hyponatremia by ingestion of hypertonic saline was followed by neurological sequelae that lead to the diagnosis of ODS. Rapid correction of hyponatremia is the most common factor for occurrence of ODS. Maximal safe range of sodium rise as therapy of hyponatremia. (less than or equal to 8-12 mmol/L in 24hours and less than or equal to 18 mmol/L in 48 hours). But the target values are lower in the range of 4-6 mmol/L/day in high risk patients. Frequent monitoring of sodium is needed in patients undergoing the treatment for hyponatremia. In this patient after the administration of treatment his motor function slowly improved after several weeks of therapy, but the emotional lability, tremor and marked deconditioning were continued[4].

ODS DUE TO SLOW CORRECTION OF HYPONATREMIA – A CASE STUDY

A case study reported 47year old non-alcoholic male came with the complaints of altered sensorium. After one week he had started ofloxacin for lower urinary tract infection and then oliguria and swelling of whole body. On general and physical examination, he presented with pedal edema, facial puffiness and mild hypertension (146/92 mmHg). In urine analysis, proteins were 100mg/dl, white blood cells were 18-20 and red blood cells were 2-4 per HPF, serum creatinine was found to be 1.8 mg/dl and diagnosed with drug-induced interstitial nephritis. The drug furosemide of

dose 60 mg daily was prescribed. On examination, the physical, systemic examination and complete blood count was normal. Serum urea was slightly increased (48 mg/dl), creatinine was also slightly increased (1.6 mg/dl). The serum electrolytes levels were normal for potassium (2.5 mmol/l), chloride (105 mmol/l) but the sodium levels were decreased (94 mmol/l) for which the normal value is 135-145 mmol/l. The patient was given with 3% Normal saline and when changed to 0.9% normal saline, the sodium level reached 120 mmol/l. Correction was done at a rate of not exceeding 8 mmol/day and the levels of sodium was reached to 135 mmol/l for a period of 8 days. Serum potassium levels were corrected with intravenous potassium chloride and patient improved. Neurological examination resulted in spastic quadriparesis, mutism and inability to swallow. MRI of brain revealed spastic quadriparesis, mutism and inability to swallow with a diagnosis of locked-in-syndrome. The patient received supportive treatment for a month when he affected with intercurrent sepsis[5].

ODS DUE TO OVERCORRECTION OF HYPONATREMIA

A study included 54-year-old male patient came with complaints of altered mental status and chronic alcoholism. He had no past history of chronic diseases except multiple presentations to emergency department for alcohol intoxication or withdrawal symptoms. He was not using any medications. On general examination vital signs were normal and Glasgow coma scale (GCS) was 15. He was alert, conscious but not oriented to the time. Laboratory assessment reported serum alcohol level of <10 mg/dl and urine drug toxicity were negative. The computed tomography (CT) scan of brain was negative for any acute symptoms and pathology. The serum electrolytes levels were as follows – serum sodium was 102 mmol/l, potassium was 2.4 mmol/l, chloride was 54 mmol/l, bicarbonate was 38 mmol/l, BUN was 8 mg/dl, creatinine was 0.62 mg/dl, magnesium was 2.2 mg/dl, phosphorous was 2.3 mg/dl, albumin was 3.6 mg/dl, alkaline phosphatase was 116 U/L, aspartate aminotransferase 117 U/L, alanine aminotransferase was 122 U/L, bilirubin was 0.9 mg/dl, the plasma osmolality was 212 mOsm/kg. The patient was given 2000 ml of 0.9% saline intravenously and the potassium level was adjusted with 40 mmol intravenously and 80 mmol through oral route. He was started with intravenous 0.9% saline infusion at a rate of 100 ml/hour. The serum concentrations were monitored periodically and serum sodium concentration was 106 mmol/l by 8 hours after admission and increased to 112 mmol/l by 16 hours, at that time 0.9 % normal saline was infused and decreased to 60 ml/hour. The regular diet was started and by 24 hours his serum sodium concentration was about 118 mmol/l. The 5% dextrose was started intravenously to reduce the sodium levels in the body at 200 ml/hour. The serum values of sodium increased by 3-4 mmol/l/day to 123-128 mmol/l from day 4-7. For the first 6 days the patient was normal and then he became somnolent and uncooperative with physical examination and suffered with urinary incontinence. The changes in speech, increased tone for upper limbs and paraplegia by day 13 of admission. The nasogastric tube was inserted as he lost swallowing capability. MRI was done on 3rd week of his admission and the report revealed pathological changes for CPM. After one month, the patient developed signs of improvement. He failed repeated swallowing evaluations and the Percutaneous Endoscopic Gastric (PEG) tube remained in place for 80 days until patient gained the capability to tolerate oral diet. In this patient the chronic alcoholism and malnutrition were contributing factors for occurrence of ODS. Regardless of initial severity of symptoms, the immediate early management id required including daily physical therapy, speech and optimal nutritional therapy including PEG replacement for seeking the early comfort measures. It takes months to respond the patient to the therapy and gain mental and functional therapy, so the immediate and aggressive treatment is required for complete recovery of the patient[6].

DISCUSSION:

ODS is a rare disease which had undetermined clinical incidence in most of the patients and diagnosed during an autopsy and MRI imaging. The initial neurological symptoms occur secondary to rapid correction of sodium. The normal correction also leads to syndrome in rare cases. The MRI scans should be followed to treat the patient. However, apart from the recent advances in clinical management, the outcomes may remain unchanged[1]. Altered sensorium was found to be the most common reason for the ODS and hypokalemia as the most common underlying factor. In an analysis, the study reported that the MRI findings revealed isolated pontine involvement in 41%, both pontine and extra pontine in 23% of cases. All the patients received the supportive therapy and of them 17 patients were completely recovered from neurological symptoms in 24% of the patients. In another study 3000 brains were examined post mortem, there were 15 cases of CPM without symptoms. The chronic alcoholism, malnutrition, psychogenic polydipsia, liver transplantation, antidiuretic hormone imbalances, dialysis and drug induced ODS are most associated factors for ODS[2]. Rapid correction of hyponatremia is a risk factor for

ODS and associated neurological sequelae. Maximal rate of sodium rise for therapy of hyponatremia should be 8-12 mmol/l or less than that value in 24 hours and less than 18 mmol/l in 48 hours. Frequent monitoring of sodium levels in patients receiving treatment for hyponatremia is required. The electronic monitoring of health records and alert of dangerous rates of increase in the levels of sodium n hyponatremia patient can help in prevention of ODS[4]. ODS can also occur due to the slow correction of hyponatremia. The demyelination can be seen within pons, extrapontine areas like basal ganglia, cerebral white matter, peripheral cortex, hippocampus and lateral geniculate bodies. Patients with ODS suffer with seizures or encephalopathy[5].

CONCLUSION:

The symptoms associated with EPM are dysarthria, dysphagia, flaccid quadriparesis which later progress to spastic, horizontal gaze paralysis, followed by coma or delirium. Based on the clinical condition of patient, the gradual correction of hyponatremia is most important step in the management of these patients. In asymptomatic patients, the plasma sodium should be increased slowly from 0.5-1. Mmol/hour and up to 10-12 mmol/L over first 24 hours. Some of the isolated case reports conclude that steroids, imidazolpyridine tartrate, plasmapheresis may be helpful in the therapy[5]. Despite of the severity of the symptoms, the immediate treatment initiation is required including electrolyte management, physical, speech, nutritional therapies. The findings should be done within short period and clinical recovery of the patient should be considered. The mental and functional capacity should be improved in the patients diagnosed with ODS and need a continuous follow up for complete recovery[7].

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