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KEY WORDS: Central pontine myelinolysis; extrapontine myelinolysis; status epilepticus.

A RARE CAUSE OF STATUS EPILEPTICUS- PONTINE AND EXTRAPONTINE MYELINOLYSIS

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ABSTRACT

Central pontine myelinolysis is a demyelinating disorder characterized by the loss of myelin in the center of the pons usually caused by rapid correction of chronic hyponatremia. The clinical features vary depending on the extent of involvement. Demyelination can occur outside the pons as well and diagnosis can be challenging if both pontine and extrapontine areas are involved. We herein report a case of myelinolysis involving pons, putamen, thalamus, external and extreme capsule and presenting as a case of status epilepticus. To the best of our knowledge, this case represents a very first case in the medical literature.

INTRODUCTION:

Central pontine myelinolysis (CPM) is a demyelinating disorder characterized by the loss of myelin in the center of the basis pontis, usually caused by rapid correction of chronic hyponatremia. On rare occasions, demyelination occurs outside the pons and is termed extrapontine myelinolysis (EPM). The term osmotic demyelination syndrome (ODS) refers to demyelination caused by changes in serum osmolality and may result in both pontine and extrapontine myelinolysis. Known risk factors for this condition include alcoholism, malnutrition, systemic medical disease, liver transplantation, and rarely, hemodialysis [1-3]. We report an unusual case of widespread CPM and EPM affecting the brain and presenting as status epilepticus. To the best of our knowledge, this case represents as very first case in the literature.

CASE REPORT:

A 54-year-old female presented to emergency department for evaluation of recurrent GTCS each episode lasting more than 5 minutes. Patient had been in bed bound state with tracheostomy in situ and was earlier diagnosed with multifactorial encephalopathy four months prior to admission. Patient was asthenic and had poor oral hygiene.Patient was managed on the lines of status epilepticus in the emergency department with first line benzodiazepine and second line anti-epileptics (Levetiracetam and Sodium Valproate).After patient did not respond to the above said medications, refractory status epilepticus was diagnosed and patient was subsequently put on inj midazolam infusion along with two anti-epileptics having different mechanism than GABA receptor modulation. Patient was monitored with continuous EEGs, therapeutic burst-suppression was maintained for at least 36 hours and subsequently tapered down the midazolam infusion under continuous EEG monitoring. Patient regained his neurological status as before the status epilepticus i.e GCS-E4V(tracheostomy)M3 with intact brainstem reflexes.

Magnetic resonance imaging (MRI)[Figure 1,2,3] of her brain revealed FLAIR/T2W hyperintensities in pons, mid-brain, symmetrical basal ganglia , external and extreme capsule. Possibility of pontine-extrapontine myelinolysis versus viral meningoencephalitis was considered. CSF study was absolutely normal. EEG [Figure 4] also did not show any focality although generalized epileptifom activity could be seen. Sodium at admission was 136 and potassium was 3.3 (low).Auto-immune profile, para-neoplastic profile, meningoencephalitis profile, anti-AQP4 antibody, Anti-MOG antibody, ANA, thyroid profile, ammonia all were negative and within normal limits respectively. CSF ACE level, VDRL were all unremarkable. CT scan of chest, abdomen, and pelvis was unremarkable. A whole body PET scan was performed, which did not reveal any abnormality. The possible cause for the pontine-extrapontine myelinolysis was considered was her malnutrition status. Thiamine supplementation and sodium were added to the management. Due to the need of long term hospitalization and bed bound state, family had arranged for supportive treatment at their place of residence and was later discharged in hemodynamically stable and neurologically status quo was achieved. Sodium level at discharge was 137.

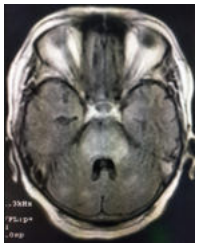

Figure 1. Showing Central pontine myelinosis (CPM).

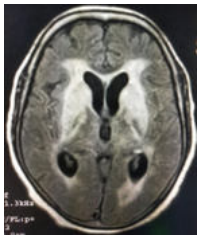

Figure 2. Showing Extrapontine myelinolysis (EPM).

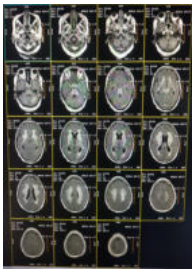

Figure 3. Showing features of CPM-EPM.

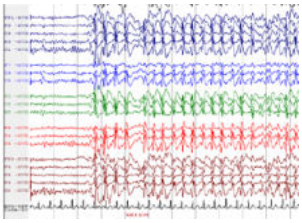

Figure 4. Showing Ongoing Active seizure activity.

DISCUSSION:

Central pontine myelinolysis (CPM) was described by Adams and colleagues in 1959 as a disease affecting alcoholics and the malnourished[1]. The concept was extended from 1962 with the recognition that lesions can occur outside the pons, so-called extrapontine myelinolysis (EPM). In 1976 a link between these disorders and the rapid correction of sodium in hyponatraemic patients was suggested, and by 1982 substantially established.

Central pontine myelinolysis (CPM)

This illness usually goes through a biphasic clinical course, initially encephalopathic or presenting with seizures from hyponatraemia, then recovering rapidly as normonatraemia is restored, only to deteriorate several days later. The initial signs of the CPM, which reflect this second phase, include dysarthria and dysphagia (secondary to corticobulbar fibre involvement), a flaccid quadriparesis (from corticospinal tract involvement) which later becomes spastic, all from involvement of the basis pontis , if the lesion extends into the tegmentum of the pons pupillary, oculomotor abnormalities may occur. There may be an apparent change in conscious level reflecting the "locked-in syndrome" that a large lesion in this site is particularly liable to produce. If lesions of EPM are also present the clinical picture may be very confusing.

Extrapontine myelinolysis (EPM)

A variety of sites may be involved (Table 1). The lesions are often strikingly symmetrical. The age of lesions in the various sites in EPM is contemporaneous. CPM and EPM are the same disease, sharing the same pathology, associations, and time course but differing in clinical manifestations.

Table 1 Lesions of central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) (in descending order of frequency)[4]

Pons
Cerebellum
Lateral geniculate body
External capsule
Extreme capsule
Hippocampus
Putamen
Cerebral cortex/subcortex
Thalamus
Caudate nucleus
The following 10% or less:
Claustrum
Internal capsule
Internal medullary lamella
Mamillary body
Medulla oblongata

Table 2. Disease states associated with CPM/EPM, often more than one association present.

Alcoholism (common)
Malnutrition (common)
After prolonged diuretic use (frequent)
Psychogenic polydipsia (rare if acute)
Burns (infrequent, and often in context of hypernatraemia)
Post-liver transplant (well recognised)
Post-pituitary surgery (rare)
Post-urological surgery/gynaecological surgery, especially if involving glycine infusions (rare)

Pathophysiology:

The pathogenesis of Osmotic Demyelination Syndrome is not clearly understood. Osmotic demyelination syndrome occurs due to depleted adaptive process to protect against brain swelling, the redistribution of solutes with correction of hyponatremia causes brain shrinkage, which leads to disruption of tight junctions and disruption of blood brain barrier causing oligodendrocyte damage and the demyelination of neurons. It has also been shown that as hyponatremia is corrected it causes down regulation of a neutral amino acid transporter and impairs cellular reuptake of amino acids, rendering them more susceptible to injury [5]. Although in this case, the possible etiology was underlying malnutrition, this CPM-EPM is usually associated with rapid correction of hyponatremia.

Table 3. Shows the recommendations from various sources on how to correct sodium.

Table 3 Published recommendations
• Too rapid is .20 mmol/l over 3 days (Norenberg)
• If Na+ ,105 mmol/l correct at 2 mmol/l/hour for first 20 mmol/l, then allow to drift to normal. If Na+ >105 mmol/l correct at 2 mmol/l/hour to 125–130 mmol/l (Ayus 1985)
• Not .12 mmol/l/day for first day, and subsequent days slower (Sterns 1987–1992)
• 2.5 mmol/l/hour and no more than 20 mmol/day (Berl 1990)
• Not 0.8 mmol/l/day (Oh 1995)
• 15 mmol/l in 24 hours (Kumar and Berl 1998)
• 10 mmol/l/day (Laureno and Karp 1997), 10 mmol/l/day in first 24 hours and less on subsequent days (Karp and Laureno 2000)
• Should not exceed 1–2 mmol/l/hour and never more than 8 mmol/l/ day (Brown 2000)
• Should not exceed 8 mmol/l on any day of correction (Adrogue, 2000)
• Although recommendations for slow correction have been standard for years, what is regarded as "slow" has changed.

Treatment based on severity of symptoms [7]

Severity	Symptoms
Moderately severe	Nausea without vomiting
	Confusion
	Headache
Severe	Vomiting
	Cardiorespiratory distress
	Abnormal and deep somnolence
	Seizures
	Coma (Glasgow Coma Scale ≤8)

Severe Hyponatremia

i.v. infusion of 150 ml 3% hypertonic over 20 min

↓

Check serum sodium concentration after 20 min while repeating an infusion of 150 ml 3% hypertonic saline for the next 20 min.

↓

We suggest repeating above steps twice or until a target of 5 mmol/l increase in serum sodium concentration is achieved.

in case of improvement of symptoms after a 5 mmol/l increase in serum sodium in the first hour- stop 3% saline and limit the increase in serum sodium concentration to a total of 10 mmol/l during the first 24 h and an additional 8 mmol/l during every 24 h thereafter until the serum sodium concentration reaches 130 mmol/l.

In case of no improvement of symptoms after a 5 mmol/l increase in serum sodium in the first hour continuing an i.v. infusion of 3% hypertonic saline or equivalent aiming for an additional 1 mmol/l per h increase in serum sodium concentration.

Hyponatraemia with moderately severe symptoms

i.v. infusion of 150 ml 3% hypertonic saline or equivalent over 20 min (2D).

↓

limit increase in serum sodium concentration to 10 mmol/l in the first 24 h and 8 mmol/l during every 24 h thereafter, until a serum sodium concentration of 130 mmol/l is reached.

↓

Check the serum sodium concentration after 1, 6 and 12 h

Acute hyponatraemia without severe or moderately severe symptoms

Cause specific treatment

If hyponatraemia is corrected too rapidly

Re-lower the serum sodium concentration if it increases >10 mmol/l during the first 24 h or >8 mmol/l in any 24 h thereafter.

It is appropriate to start an infusion of 10 ml/kg body weight of electrolyte-free water (e.g. glucose solutions) over 1 h under strict monitoring of urine output and fluid balance.

Status Epilepticus

A seizure that lasts longer than 5 minutes, or having more than 1 seizure within a 5 minutes period, without returning to a normal level of consciousness between episodes is called status epilepticus. This is a medical emergency that may lead to permanent brain damage or death [8-11].

There are multiple etiologies for status epilepticus [12]
Potential acute processes include:

- Central nervous system (CNS) infections (meningitis, encephalitis, and intracranial abscess)
- Metabolic abnormalities (hypoglycemia, hyponatremia, hypocalcemia, hepatic encephalopathy, and inborn errors of metabolism in children)
- Cerebrovascular accidents
- Head trauma (with or without intracranial bleed)
- Drug toxicity
- Drug withdrawal syndromes (e.g., alcohol, benzodiazepines, and barbiturates)
- Hypoxia
- Hypertensive emergency
- Autoimmune disorders

Chronic processes that may result in status epilepticus include pre-existing epilepsy with breakthrough seizures or non-compliance with anti-epileptic drugs, ethanol withdrawal, CNS tumors, and remote CNS pathology (e.g., traumatic brain injury, stroke).

Acute processes account for most cases of status epilepticus in adults. Febrile status epilepticus is the most common cause in pediatric patients. CNS infections and inborn errors of metabolism are also common etiologies in children. The majority of pediatric patients with the first presentation of status epilepticus have no previous history of seizures.

Investigations:

Evoked potentials and Imaging:

Before computed tomography (CT) brainstem auditory evoked potentials were used, but modern imaging has superseded its use.

CPM can be seen on CT, but magnetic resonance imaging (MRI) is frequently striking (fig 5) and is the imaging technique of choice, having a greater sensitivity for CPM than CT and superior capacity for the demonstration of the lesions of EPM. Hyperintense lesions are seen on T2, and hypointense lesions on T1 weighted images. The lesions are non-contrast enhancing.

The timing of the appearance of lesions on MRI may be significantly delayed, and if the diagnosis remains likely a repeat imaging study at 10–14 days may reveal lesions not apparent on early scans.

Treatment of CPM/EPM and potential future therapies:

At present supportive treatment is all that can be recommended with certainty.

Reports on small case series or single case reports of treatments including steroids, intravenous immunoglobulin, and thyrotrophin releasing hormone, have all shown good outcomes but are difficult to interpret for the above reason. Intriguing is the possible benefit of reinducing hyponatraemia, as has been reported in animal studies and two human cases [6].

PROGNOSIS:

An individual prognosis is difficult. Neither clinical features nor extent of radiological change are predictive. In summary, the outcome may be death, disability, or recovery to a virtually normal level of function.

Table 4. Osmotic demyelination syndromes: key points

- Consider in a patient who has failed to recover as expected after a severe illness requiring intravenous fluids.
- Consider in a patient manifesting "psychiatric" symptoms after such an illness, even if imaging is negative.
- Na+ rise need not be in excess of 10 mmol/l/day for condition to develop. There may be no "safe" limit for the rate of Na+ rise; readers would be prudent to review recommended limits of acceptable Na+ rise at regular intervals as the recommended limit has steadily fallen.
- Prognosis is not uniformly bad
- MRI changes may be delayed
- MRI severity is not prognostic
- Extra-pontine myelinolysis may manifest in a number of different ways, the clinical picture can evolve over days, and some of the manifestations may be symptomatically treatable

CONCLUSIONS:

This case represents an extremely devastating/disabling neurological illness which can be potentially prevented if all the necessary steps are taken accordingly while correction of sodium or malnutrition or other measures to optimize the conditions which case CPM-EPM. Although seizures are common in such a condition, but in this current case although sodium was normal throughout the course, patient had presented to emergency in status epilepticus and to the best of our knowledge this is probably the first case of status epilepticus secondary to CPM-EPM in medical literature.

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