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Case Report

A case of Acute Disseminated Encephalomyelitis with Syndrome of Inappropriate Antidiuretic Hormone Secretion

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Introduction

The kidney and the brain play a key role in water and sodium homeostasis in the extracellular fluid. Hyponatremia is a commonly encountered electrolyte abnormality in patients with central nervous system disorders [1]. In neurological disorders involving the brain, disrupted osmoregulation will result in cerebral oedema and elevated intracranial pressure due to the hypoosmolality caused by hyponatremia [1]. The two main causes of hyponatremia, excluding iatrogenic causes, are syndrome of inappropriate ADH secretion (SIADH) and cerebral salt wasting.

Acute disseminated encephalomyelitis (ADEM) is a post-infectious, immune-mediated, demyelinating disorder of the central nervous system with a predilection to early childhood. It gives rise to widespread inflammation of the white matter of the brain and spinal cord. Though it lacks a definite marker for diagnosis, the clinical presentation and neuroimaging, mainly MRI, assist in the diagnosis. It is typically a monophasic disease with a preceding history of febrile illness. The patient presents with features of encephalopathy of varying degrees. Susceptibility to ADEM is determined by multiple factors including genetic predisposition, prior exposure to infectious agents and age [2]. The commonly encountered neurological manifestations include confusion, unsteadiness, visual blurring, dysphagia and unilateral body weakness [3]. SIADH is a state which results from unsuppressed ADH secretion presenting as hypoosmolality and hyponatremia with predominantly neurological sequelae. The mainstay of treatment is restriction of fluids [4]. Refractory cases necessitate

more sophisticated medical treatment modalities. It should be always borne in mind that rapid sodium correction can lead to central pontine myelinolysis [4].

Case presentation

A 65-year-old South Asian gentleman with a past history of Type 2 diabetes mellitus for 10 years, hypertension, ischaemic heart disease and epilepsy, presented with subacute onset of right sided face, arm and leg weakness with a reduced level of consciousness for 3 days duration. He had a recent prodromal febrile illness with coryzal symptoms lasting for 3 days 2 weeks previously. The clinical condition had progressively deteriorated over the course of 3 days. His bladder and bowel functions were, however, preserved.

On examination, the Glasgow coma score was 11/ 15 (eye opening 3/4; verbal 4/5; motor 4/6), He was afebrile and not pale or icteric. There was no neck stiffness and Kernig's sign was absent. The hydration status was good (euvolaemic). He had no lymphadenopathy, ankle oedema or peripheral stigmata of chronic liver cell disease. On neurological examination, there was right sided upper and lower limb spastic hemiparesis with an upgoing plantar and preserved sensation. No cranial nerve involvement was detected. Cerebellar signs were absent with spared bladder and bowel function. Fundoscopic examination revealed diabetic pre-proliferative retinopathy. Cardiovascular examination revealed a blood pressure of 140/ 90 mmHg and a heart rate of 96 beats per minute that was regular with good volume. The abdomen and respiratory examinations were unremarkable. Investigations are shown in Table 1. Neuromyelitis optica spectrum disorder antibodies were negative. MRI brain [Figure 1] is shown below.

Table 1: Investigations

Test	Reference values	Results on admission	Results after 1 Week
Full blood count			
White cell count (10^3/ µl)	4- 11	21.54	10.1
Neutrophils 10^3/ µl	2- 7	18.26	7.1
Lymphocytes 10^3/ µl	1- 5	1.98	1.2
Eosinophils 10^3/ µl	< 0.5	0.05	0.03
Monocytes 10^3/ µl	0.2- 0.8	1.22	1.4
Platelets 10^3/ µl	150- 400	395	398
Hemoglobin g/dl	11- 15	14.3	14
CRP mg/l	< 5	25	4
ESR mm/hr	< 22	21	
LDH U/L	< 234	210	
Serum Na^+ mmol/l	135- 145	120	132
Serum K^+ mmol/l	3.5- 5.1	4	3.9
Serum osmolality mosm/ kg	275-295	267	
Urine sodium mmol/ L	< 20	36	
Urine osmolality mosm/kg	50-1200	652	
Serum Ca^{2+} mmol/L	2.1- 2.6	2.2	
Serum creatinine µmol/L	100- 115	144	140
Blood urea mmol/L	3- 7	7.1	7

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ALT U/L	10- 50	22	23
AST U/L	10- 40	24	28
ALP U/L	25- 150	66	64
Gamma- glutamyl transferase U/L	10 - 65	43	40
Total protein g/l	65- 83	68	66
Serum albumin g/l	35- 50	40	41
Serum globulin g/l	20- 40	28	25
Total bilirubin µmol/L	5- 17	8	10.7
INR	< 1.1	0.3	
Cerebrospinal fluid appearance	Clear	Clear	
Cerebrospinal fluid protein mg/dl	< 40	20	
Cerebrospinal fluid glucose mg/dl	1/2 to 2/3 of the RBS	132	
Random blood glucose mg/dl	< 180	220	
Cerebrospinal fluid red cells / mm^3	Nil	10	
Cerebrospinal fluid polymorphs /mm^3	Nil	Nil	
Cerebrospinal fluid lymphocytes / mm^3	< 5	3	
Cerebrospinal fluid IgG index	< 0.7	0.1	
Cerebrospinal fluid oligoclonal bands		Not detected	
Cerebrospinal fluid TB culture		No growth	
Cerebrospinal fluid culture		No growth	
Free thyroxine ng/dl	1-1.7	1.2	
TSH mIU/ L	10- 28	14	
9 am cortisol nmol/L	140-600	185	
Serum uric acid mg/dl	3.5- 7	3.2	
APTT	30-40 seconds	22	
UFR: Pus cells	Nil	15- 20/ hpf	
UFR: Red cells	Nil	1-2/ hpf	
UFR: Albumin	Nil	Nil	
Blood Culture		No growth	
Urine Culture		Mixed growth	No growth
Blood picture		Normal	
ECG		Sinus rhythm	
2D echocardiography		Ejection fraction: 60% with normal valves	
US abdomen		Acute renal parenchymal changes No hepatosplenomegaly or lymphadenopathy	

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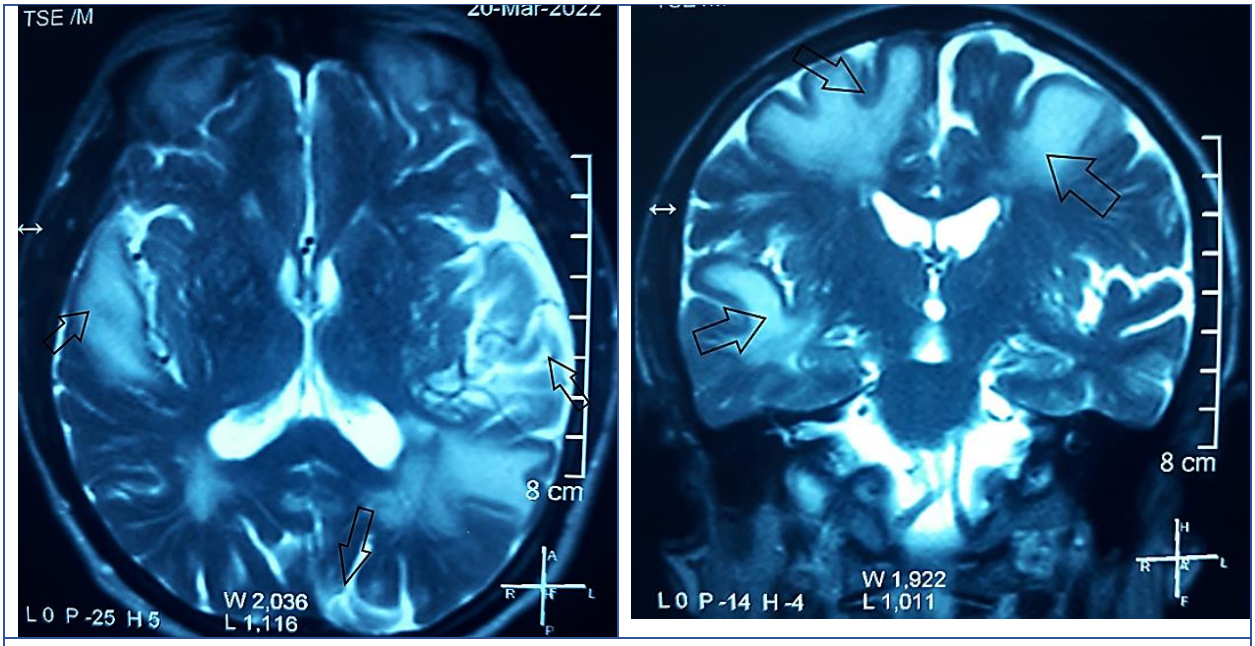

Figure 1: MRI brain showing multiple white matter regions of high T2 signals identified in both frontal, parietal and temporal lobes

MRI brain showed multiple white matter regions of high T2 signals in frontal, parietal and temporal lobes. Some lesions showed restricted diffusion at the edges of the lesions with no central restricted diffusion. No significant mass effects were seen. Appearance is likely due to ADEM.

He was started on intravenous methylprednisolone 1 gram daily for 5 days. He was treated with intravenous co-amoxiclav 1.2 g three times daily for a possible urinary tract infection. Hyponatremia was managed with strict fluid restriction (1.5 litres per day) and by omitting enalapril. A strict input-output chart was maintained and the patient passed around 2 litres of urine per day. Oral salt was added for correction of hyponatremia. Basal bolus insulin regimen was started for glycaemic control. His routine medications were continued and did not include any diuretics. The patient showed a good response to the treatment and his conscious level improved in 3 days and he returned to full mobility on day 7 of treatment.

Discussion

The clinical diagnosis of ADEM was made on the basis of multiple demyelinating lesions on the MRI brain along with clinical findings showing multifocal neurological deficits following a prodromal febrile illness. ADEM results from an abnormal immune response to an infection or other inciting agent, although the pathogenesis is not clearly described [5]. ADEM most often follows viral infections though, in some cases, it may be secondary to bacterial infections or immunization [5]. The mainstay of treatment is high dose steroids. It displays a phenomenal response if the appropriate management is initiated promptly [5]. Refractory

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cases may necessitate either intravenous immunoglobulin or total plasma exchange as second line therapy [5].

Although ADEM is characteristically a monophasic illness, it can be the first presentation of multiple sclerosis or neuromyelitis optica spectrum disorder [6]. However, the absence of aquaporin 4 receptor antibodies, anti-myelin oligodendrocyte glycoprotein antibodies (MOG- Ab) and oligoclonal bands in the cerebrospinal fluid makes those scenarios unlikely in the index patient. A prolonged follow-up is nonetheless warranted because these disorders are often polyphasic [6].

Hyponatremia is common in a variety of neurological disorders and could be due to SIADH or cerebral salt wasting. Accurate distinction of these entities is important due to differences in management. To arrive at a diagnosis of, the volume status of the patient at presentation was strongly considered. The patient was euvolaemic in fluid status with hyponatremia and associated hypoosmolality and increased urine sodium and osmolality which favoured the diagnosis of SIADH over cerebral salt wasting [7]. We excluded hypothyroidism and Addison's disease before making the diagnosis. In cerebral salt wasting, the patient is often dehydrated and is usually polyuric, features which were not observed in our case [7]. The treatment of these two conditions follow entirely different courses. The initial treatment of SIADH is fluid restriction whereas cerebral salt wasting requires replacement of fluid and electrolytes [7]. Our patient demonstrated significant clinical improvement with fluid restriction which again tilts the diagnosis in favor of SIADH.

Both SIADH and cerebral salt wasting are associated with a low uric acid level. Low uric acid is attributed to the expanded volume in SIADH whereas it is thought to be due to reduced sodium reabsorption in the proximal convoluted tubules in cerebral salt wasting [8]. Some recommend the change in uric acid excretion in response to sodium correction as a marker for differentiation. Nevertheless, without a defined target for volume depletion, it is difficult to accept it as a surrogate marker [8].

SIADH occurs due to the unregulated secretion of vasopressin and is secondary to many causes such as infections of the brain, lung and other regions, certain medications and some neoplasms [9]. The mainstay of management is fluid restriction. When it is resistant to initial therapy, pharmacological agents should be used. They are mainly demeclocycline (a tetracycline) and tolvaptan (a selective vasopressin V2 receptor antagonist) [9]. Careful monitoring of the treatment response with regular serum sodium levels is advised when using these agents [9]. Hypertonic saline administration is indicated only in highly symptomatic patients, such as those with seizures due to the rapid decrease in sodium concentration, [9].

A case of co-existing cerebral salt wasting and ADEM was reported in 2012 [10]. In that instance, the volume status, levels of natriuretic peptide and changes in the fractional

excretion of urate with sodium correction helped to differentiate between cerebral salt wasting and SIADH [10]. There were instances of encephalopathy and hyponatremia in patients with COVID- 19 [11]. There are case reports reporting the association of neuromyelitis optica and hyponatremia in children [12]. The osmotic demyelination syndrome secondary to hyponatremia is reported to be connected with demyelination disorders such as neuromyelitis optica in an adolescent. There are other cases of neurological involvement associated with hyponatremia [13]. There are cases of symptomatic hyponatremia following lateral medullar infarct [14]. But there are some rare case reports recording neurologically asymptomatic patients with severe hyponatremia [15].

Conclusion

The association of ADEM and SIADH, though rare, needs to be managed appropriately since both of them contribute to the neurological manifestations. Intravenous corticosteroids along with fluid restriction is the key to a successful recovery.

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