CASE REPORT

CEREBRAL INFARCTION AND CEREBRAL SALT WASTING SYNDROME IN A PATIENT WITH TUBERCULOUS MENINGOENCEPHALITIS

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Abstract. A 38-year old female with underlying systemic lupus erythematosus was admitted with tuberculous meningoencephalitis. After an initial good response to anti-tuberculous treatment, she developed cerebral infarction and profound hyponatremia. This was due to cerebral salt wasting syndrome, which has only previously been described in 2 cases. The difficulties in diagnosis and management of this case are discussed.

Cerebral infarcts can occur in 13.5-47% of patients with tuberculous meningitis (Hsieh *et al*, 1992; Verdon *et al*,1996; Brutto, 1998; Ozates *et al*, 2000; Lan *et al*, 2001). Patients with cerebral infarcts have a mortality rate three times higher than patients without infarcts (Leiguarda *et al*, 1988). Hyponatremia commonly complicates a number of intracranial disorders, including head injury, tumors, intracranial infection and stroke. A number of reports have shown that hyponatremia in many patients with intracranial disorders may actually be caused by the cerebral salt wasting syndrome (CSW), in which renal loss of sodium leads to hyponatremia and hypovolemia (Oster *et al*, 1983; Nelson *et al*, 1984; Ti *et al*, 1998). This report describes a case of tuberculous meningoencephalitis complicated by cerebral infarction and cerebral salt wasting syndrome and discusses the management of such cases.

KST, a 38-year-old Chinese female, was diagnosed as having systemic lupus erythematosus (SLE) with lupus nephritis (World Health Organization class II) in 1989. She was treated with prednisolone, ranging from 10 to 15 mg, daily. She was admitted to a district general hospital with a 10-day history of fever, headache, vomiting and abnormal behavior and found to have neck stiffness and papilledema. Lumbar puncture reported a total white blood cell count of 16/μl with 90% lymphocytes, protein 1.1 g/l, sugar 1.4 mmol/l, Indian ink and acid-fast bacilli staining negative. She was treated for bacterial meningitis with intravenous benzylpenicillin and cefepime as well as oral prednisolone 30 mg daily. However, her general condition and neurological status deteriorated despite one week of treatment. She was subsequently transferred to our hospital University Malaya Medical Centre for further management.

On arrival, the patient was drowsy with a Glasgow Coma Scale (GCS) score of 8/15 (motor 5, eye 1, verbal 2). The pupils were 3 mm and reactive to light bilaterally. There was conjugate eye deviation to the left and severe neck stiffness. Her vital signs were as follows: blood pressure 150/80 mmHg, pulse rate 90/minute with regular rhythm and temperature 38ºC. Cardiovascular, respiratory and abdominal systems examinations were normal. In the neurological examination, muscle tone was normal but her deep tendon reflexes were generally depressed with bilateral down-going plantar reflexes. Results of investigations on admission were: hemoglobin 12.6 g/dl, total white cell count 13.2×10^9/l (neutrophil

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83%, lymphocyte 8%, monocyte 8%, eosinophil 1%), ESR 36 mm/hour, serum sodium 134 mmol/l, potassium 3.5 mmol/l, chloride 90 mmol/l, carbon dioxide 24.8 mmol/l, urea 3.9 mmol/l, creatinine 49 μmol/l, total protein 75 g/l, albumin 28 g/l, normal liver function tests, calcium 1.97 mmol/l, phosphate 0.8 mmol/l, magnesium 0.7 mmol/l, coagulation profile normal. Her lumbar puncture results were as follows: opening pressure 32 cm H_2O, white cell count 90/μl (polymorphonuclear cells 33%, lymphocytes 67%), red blood cells 20/μl, protein 1.59 g/l, glucose 0.5 mmol/l, gram staining negative, Ziehl-Nielsen stain negative, Indian ink stain negative, cryptococcal antigen negative. Serum cryptococcal antigen was negative. Blood cultures were negative. Urinalysis was normal. Her IgG anticardiolipin antibody titer was 7 IU/l [normal range (NR) 0-6] and lupus anticoagulant was negative. Complement levels were normal, C3 100 mg/dl (NR 86-184), C4 20 mg/dl (NR 20-59). The antinuclear antibody titer was high at 1:1250 and anti double-stranded DNA antibody was also elevated 125 U/l (NR 0-200). The chest X-ray was normal. Computed tomography (CT) of the brain with contrast showed a non-enhancing hypodense area in the region of the corpus callosum and also within the genu of the left internal capsule (Fig 1). A presumptive diagnosis of tuberculous meningoencephalitis was made based on the CSF findings. She was treated with standard anti-tuberculous drug therapy, consisting of isoniazid, rifampicin, pyrazinamide and streptomycin. She was given intravenous hydrocortisone 100 mg qds for her SLE, as well as fluid, electrolyte and enteral nutritional support.

The patient initially improved clinically and was fully conscious and orientated, although still drowsy after 5 days of anti-tuberculosis treatment. However, her conscious level deteriorated 3 days later to a GCS score of 4/15 (motor 2, eye 1, verbal 1). Her pupils were 3 mm reactive to light bilaterally. Her blood pressure dropped to between 80-90 systolic and between 50-60 diastolic. She had a tachycardia of 100-120/minute, regular rhythm. There was no neck stiffness and no new neurological signs. Her blood investigations at this point showed the following: serum sodium 112 mmol/l, potassium 4.3 mmol/l, chloride 80 mmol/l, urea 2.4 mmol/l, creatinine 44 mmol/l, corrected calcium 2.02 mmol/l, magnesium 0.65 mmol/l, serum osmolality 276 mosm/kg, urine osmolality 280 mosm/kg and urinary sodium 148 mmol/l. Her arterial blood gases results were as follows: PO_2 14.9 kPa, PCO_2 4.6 kPa, pH 7.41. Magnetic resonance imaging of the brain revealed similar findings to the earlier CT scan (Fig 1). It was therefore assumed that her reduced conscious level was due to the profound hyponatremia. She was in negative fluid balance in the day prior to the deterioration with a total (intravenous and oral) input of 2,700 ml compared to a total urinary output of 2,800 ml. In the next 24 hours, the patient developed diuresis, with urine output increasing from 100 to 200 ml/hour and a low central venous pressure, despite adequate fluid replacement. It was felt that the patient had hypovolemic shock secondary to diuresis and renal sodium loss. For the subsequent 20 days, the patient had a total urine output of 4-5 liters per 24 hours and needed similar amounts of total fluid input daily, consisting of nasogastric feeding and intravenous saline to maintain her blood pressure at about 100/70 and her central venous pressure between 8-10 cm^3 H_2O. The serum sodium increased to 120 mmol/l with the use of saline infusions and stabilized at 130-135 mmol/l. Her conscious level improved with the correction of the serum sodium level. On day 20 of anti-tuberculosis treatment, the patient was fully conscious, orientated to time, person, place and able to walk with minimal assistance. The patient was discharged on day 37 of anti-tuberculous treatment with oral prednisolone.

The patient was admitted to her local district general hospital 2 weeks after completing the 2-month intensive phase of anti-tuberculosis treatment. She presented with fever, vomiting, and progressive reduction in her level of consciousness. She was subsequently transferred to our hospital, University Malaya Medical Centre. On arrival, her GCS score was 7/15 (motor 3, verbal 1, eye 3). There was conjugate eye deviation to the left, papilledema, flexion of right upper and lower limbs to pain stimuli, generalized hyperreflexia and bilateral up-going plantar reflexes. A CT scan of the brain revealed massive cerebral infarction in the right middle cerebral artery ter-

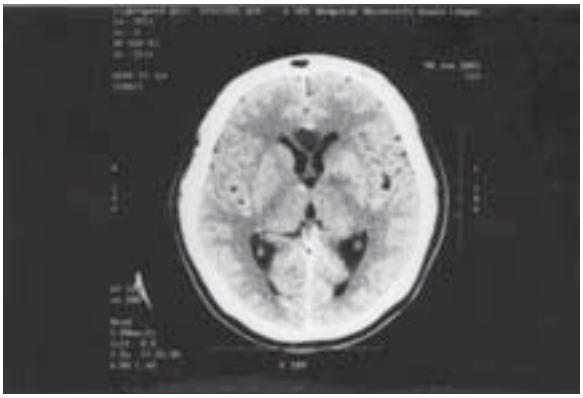

Fig 1– Contrast-enhanced CT at the level of the third ventricle shows non-enhancing hypodense area in the region of the corpus callosum. Subtle hypodense area seen within the genu of the left internal capsule.

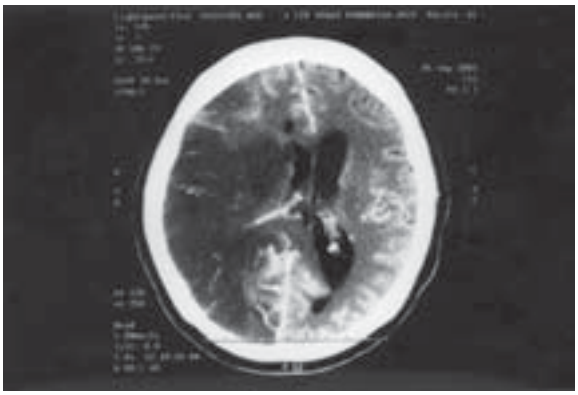

Fig 2– Post-contrast-enhanced CT, done 6 weeks after admission, showing cerebral infarct in the right middle cerebral artery distribution with mass effect and shift of midline with associated hydrocephalus. An area of hypodensity seen at the right frontal horn is suggestive of an old infarct.

ritory (Fig 2). She was intubated and ventilated. Unfortunately, the patient succumbed 2 days later to raised intracranial pressure and coning.

In summary, this patient had tuberculous meningoencephalitis based on her CSF findings and a good clinical response to anti-tuberculous treatment. Her tuberculous meningoencephalitis was complicated by cerebral infarction secondary to tuberculous angiitis involving the right middle cerebral artery, leading to the CSW syndrome, *ie* hyponatremia and hypovolemia due to urinary loss of water and sodium, with dramatic response to water and salt replacement.

Hyponatremia is a common complication of intracranial insults, including head trauma, infection and cerebrovascular accidents. Severe hyponatremia, especially with a rapidly falling sodium level, can lead to confusion, lethargy, seizure and coma. Early determination of the etiology for hyponatremia leading to effective treatment is critical for hyponatremic patients with intracranial disease, because when severe hyponatremia is overcorrected or corrected too rapidly, central pontine myelinosis and death can result. Hyponatremia in the patient with intracranial pathology is often attributed to inappropriate secretion of antidiuretic hormone (SIADH). However, a number of studies and case reports have shown that hyponatremia in many patients with intracranial disease may actually be caused by CSW, in which a renal loss of sodium leads to hyponatremia and a decrease in the extra and intravascular fluid volume (Oster *et al*, 1983; Nelson *et al*, 1984; Harrigan, 1996; Ti *et al*, 1998). It was felt that our patient had CSW based on the clinical picture of profound hypovolemia associated with hyponatremia and increased urinary sodium loss, which responded to fluid replacement. Although well described in patients with intracranial insults, to our knowledge, CSW have only been described in 2 other cases of tuberculous meningitis (Oster *et al*, 1983; Ti *et al*, 1998). It is suggested that CSW be considered in the differential diagnosis of hyponatremic patients with tuberculous meningitis.

Other causes of hyponatremia that should be considered in a patient with intracranial disease include iatrogenic fluid overload or diuresis, congestive cardiac failure, liver or renal diseases, hypothyroidism, adrenal insufficiency and artifactual hyponatremia resulting from hypercholesterolemia or hypertriglyceridemia. These causes were unlikely in our patient as she had normal liver and renal function, normal lipid profiles and evidence of hypovolemia with nearly normal serum osmolality. In addition, she was on high dose steroid treatment, thus excluding the possibility of Addison's disease as a cause for her hyponatremia. Because most patients with CSW seem to

meet the criteria for SIADH, a thorough clinical examination and laboratory evaluation is necessary to distinguish between the two. Measurement of intra- and extra-vascular fluid volume is critical. A decrease in intra- and extra-vascular volume, a negative salt and water input:output ratio are the most important factors distinguishing CSW from SIADH. The patient with CSW responds to salt and volume replacement rather than restriction, an important difference in the management of such patients.

The mechanism of CSW is not clearly defined. Both humeral, primarily excessive atrial natriuretic peptide secretion, and neural mechanisms, which influence renal sodium reabsorption following intracranial insults, are believed to be important factors leading to CSW (Harrigan, 1996).

It remains difficult to make an early diagnosis of tuberculous meningoencephalitis. In patients with SLE, the problem is compounded by the fact that active SLE can mimic the symptoms of tuberculous meningoencephalitis and vice versa. This could lead to a delay in diagnosis and starting treatment, with severe consequences. The outcome of TB meningitis has been shown to be poorer when treatment is delayed, even for as little as 3 days (Verdon *et al*, 1996).

Pathologically, tuberculous meningoencephalitis is characterized by the formation of a thick leptomeninges exudate that encroaches on the structures located at the base of the brain, including the cranial nerves and the arteries forming the circle of Willis and their penetrating branches (Dastur, 1972). This arterial involvement usually results in inflammatory changes within the vessel walls that will cause arterial narrowing and subsequently cerebral infarcts. The main histological changes observed in tuberculous angiitis include: inflammatory infiltration of the wall of small and medium-sized arteries, fibrinoid and hyaline degeneration of the intima, subendothelial cellular proliferation with narrowing and occlusion of the lumen, and perivascular cuffing of lymphocytes. Cerebral infarcts can occur in up to 47% of patients with tuberculous meningitis (Hsieh *et al*,1992; Verdon *et al*, 1996; Brutto, 1998; Ozates *et al*, 2000; Lan *et al*, 2001) and thus represents one of the serious complications of this condition, as patients with cerebral infarcts have a poorer outcome (Kalita and Misra, 1999). Most infarcts are small and located in the territory of the lenticulostriate branches of the middle or anterior cerebral artery, and may be bilateral or symmetrical in some cases (Hsieh *et al*, 1992). Large infarcts involving the whole territory of the middle cerebral artery have also been reported (Bhargava *et al*, 1982). The tuberculous angiitis is an area of tuberculous cerebritis or myelitis within the brain that joins to form a mature non-caseating tuberculous granuloma and may appear as a circumscribed area of low attenuation without post-contrast enhancement on CT scan (Shah, 2000), as seen in our patient.

In our patient, although the Ziehl-Nielsen stain of the CSF was negative, the other CSF findings, raised protein and low glucose levels and lymphocytosis, were suggestive. In addition, she had SLE and was therefore immunocompromised. A presumed diagnosis of tuberculous meningoencephalitis was made and anti-tuberculous treatment started. She improved on treatment, suggesting that the diagnosis was correct. From the first admission CT scan, she already had hypodense areas on her scan, suggestive of tuberculous angiitis, or small cerebral infarcts. It was felt that the cerebral infarct was likely due to tuberculous angiitis, since the SLE disease activity in our patient was quiescent, both serologically and clinically. In addition, her anticardiolipin antibody and lupus anticoagulant tests were negative, *ie* there was no suggestion of an associated antiphospholipid syndrome that could have caused the cerebral infarcts. Cerebral infarcts have been shown to occur at any time during the course of tuberculous meningitis (Lan *et al*, 2001). It is unknown why only certain patients with tuberculous meningitis develop cerebral infarcts and no specific treatment has been shown to reduce this complication. Unfortunately, despite all medical therapy, mortality in patients with cerebral infarcts secondary to tuberculosis is three times higher than that of patients without infarcts (Leiguarda *et al*, 1988).

In conclusion, it is important to maintain a high index of suspicion for the diagnosis of tuberculous meningoencephalitis, as early treatment gives the patient the best chance of success. In

addition to the common problem of SIADH, CSW has to be considered in the differential diagnosis of such patients with hyponatremia as the management of the two conditions is diametrically opposite.

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