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## LETTER TO THE EDITOR

# SEPSIS-ASSOCIATED ENCEPHALOPATHY AS A DIFFERENTIAL DIAGNOSIS WITH MOTOR DEFICIT PLUS ALTERED MENTAL STATUS

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## INTRODUCTION

Sepsis-associated encephalopathy (SAE) is a poorly understood and underdiagnosed neurological complication of sepsis. Several conditions commonly associated with sepsis (hepatic or renal dysfunction, electrolyte abnormalities, acid-base disturbances, glycemia disturbances, hypotension, hypoxemia, sedation, body temperature disturbances, and neuroendocrine dysfunction) make SAE evaluation difficult.

Sepsis-associated encephalopathy has been reported to occur in 8% to 70% of septic patients. This large range derives from the different definitions of sepsis and encephalopathy used in the current literature.[1] In some cases, SAE may precede other manifestations of sepsis.[2] We report a case of a 37-year-old pregnant woman who developed septic encephalopathy for whom the initial symptom was confusion that evolved with motor deficit and subsequently to coma.

## CASE REPORT

A 37-year-old woman, 27-weeks pregnant, was transferred to the emergency department of Hospital das Clínicas de São Paulo due to altered mental status. According to her husband, approximately 3 hours earlier that morning soon after she woke up, the patient was confused and repeatedly uttering inappropriate words.

The patient had had 2 previous hospitalizations in the previous 2 months for investigation of anasarca. On examination, an abdominal ultrasonography revealed dilated portal system veins, hepatomegaly with left lobe predominance, and splenomegaly.

During the same hospitalization, a feces exam was performed (Table 1), and the diagnosis of portal system hypertension and nephrotic syndrome due to schistosomiasis was made. Moreover, she presented anemia secondary to the nephrotic syndrome and pyelonephritis by *Enterococcus sp*. She was discharged to her home taking furosemide 40 mg/d, enoxaparin 40 mg/d, vitamins, and alimentary supplements (folic acid, B-complex vitamins, and ferrous sulfate). It was her fourth gestation, and the previous ones had evolved well; her children were 15, 10, and 7 years old.

**Table 1 -** Laboratory exams

| | Normal Range | Results |
|---|---|---|
| **Blood** | | |
| Ammonia (µg/dL) | 19-87 | 56 |
| Thyroxine free (ng/dL) | 0.7-1.5 | 0.84 |
| TSH* (µU/mL) | 0.4-4.5 | 1.55 |
| **Feces** | | |
| Kato-Katz# (eggs/g of feces) | 0 | 24 |

* TSH: thyroid stimulating hormone
\# Kato-Katz: egg counts of *Schistosoma mansoni* – Kato-Katz technique

After 3 days, she was transferred again to the hospital.

**Day 1.** At physical examination, the following was observed: Glasgow Coma Scale (GCS) = 13 (best eye response (BER) = 4, best motor response (BMR) = 6, best verbal response (BVR) = 3); isocoric pupils with a prompt reaction to light and no focal neurological signs; jaundice, 2+/4; pale mucosa; and edematous limbs. Her heart rate was 120 bpm, blood pressure was normal (130 x 80 mm Hg), lung auscultation was normal, and she was eupneic. The measurement of uterine fundal height was 20 cm and fetal heart sounds were present. On the same day, there was a decreased GCS to 9 (BER = 2, BMR = 5, BVR= 2), but without other alterations of the physical examination. A cranial computed tomography (CT) was performed with normal results. After the CT procedure, cerebrospinal fluid was obtained (Table 2).

**Day 2.** The patient remained with normal blood pres-

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**Table 2 -** Cerebrospinal fluid

| | Normal Range | Results |
|---|---|---|
| Cells: | ≤ 5 cells/mm³ | 1/mm³ |
| Red blood cells: | 0 cells/mm³ | 55/mm³ |
| Lymphocytes: | | 64 % |
| Monocytes: | | 2 % |
| Neutrophils: | | 34 % |
| Proteins: | ≤ 40 mg/dL | 13 mg/dL |
| Glucose: | 50-90 mg/dL | 42 mg/dL |
| Chloride: | 118-140 mEq/L | 123 mEq/L |
| Cultures: | negatives | negatives |
| Indian Ink: | negative | negative |

sure, and her heart rate was 125 bpm. However, GCS decreased to 8 (BER = 2, BMR = 4, BVR = 2), downward conjugate movement of the eyes was noticed as well as incomplete right hemiparesis, even though sedatives were not used. The patient was transferred to the intensive care unit, and sedation with midazolam was performed to carry out an orotracheal intubation. Soon after orotracheal intubation, the blood pressure was normal, and cultures of blood and urine were collected. Laboratory results are listed in Tables 1 and 3. Intravenous fluid was administrated due to worsening renal function (Table 3). The chest x-ray revealed alveolar infiltrates in the left lower lobe.

**Day 3.** At 11:30 AM, the obstetric ultrasonographic examination revealed fetal death. Neurologic examination remained the same and the blood pressure was 136 x 100 mmHg.

**Day 4.** At 00:30 AM, she presented agitation, high blood pressure (168 x 100 mm Hg), tachycardia (163 beats per minute), tremor, and sweating. This was followed by fever (37.9°C) and hypotension (80 x 40 mm Hg), with prompt response to infusion of 2 liters of crystalloids. On the same day, purulent tracheal sputum was noticed, associated with a decrease in the $PaO_2/FiO_2$ ratio (Table 3). Antibiotic therapy was introduced, initially with cefepime plus clindamycin, to treat possible lung or pelvic infections. At 3:30 AM, spontaneous fetal expulsion occurred; the fetus was dead and without fetid odor. The placenta was normal. The patient's physical examination revealed a GCS 7T (BER = 2, BMR = 4, BVR = 1 and T = orotracheal intubation), absence of conjugate eye movement and hemiparesis. She was anicteric with anasarca. The electroencephalogram (Figure 1) suggested metabolic disturbances (excess of slow waves and presence of triphasic waves). The magnetic angioresonance and cerebral parenchyma magnetic resonance images were normal.

**Day 5.** The urine culture collected at day 2 was grow-

**Table 3 -** Daily laboratory results

| | Normal Range | Day 1 | Day 2 | Day 4 | Day 5 | Day 8 | Day 11 |
|---|---|---|---|---|---|---|---|
| Sodium (mEq/L) | 135-145 | 137 | 137 | 137 | 139 | 144 | 146 |
| Potassium (mEq/L) | 3.5-5.0 | 3 | 3.8 | 3.4 | 3.4 | 2.8 | 3.5 |
| Magnesium (mg/dL) | 1.58-2.55 | 2.58 | 2.58 | 2.24 | 2.05 | 1.83 | 1.76 |
| Chloride (mEq/L) | 96-105 | - | 106 | 105 | 108 | 117 | 116 |
| Glucose (mg/dL) | 70-100 | 68 | 98 | - | 96 | 77 | 81 |
| Phosphorus (mg/dL) | 2.7-4.5 | - | 4.7 | 5.1 | 4.1 | 3.1 | 2.8 |
| Total Bilirubin (mg/dL) | 0.2-1.0 | 1.9 | 1.7 | 1.5 | 0.8 | 0.6 | 0.6 |
| Direct Bilirubin (mg/dL) | < 0.3 | 1.2 | 1.2 | 1.0 | 0.3 | 0.3 | 0.3 |
| Creatinine (mg/dL) | 0.5-0.9 | 1.23 | 2.13 | 1.73 | 1.33 | 0.83 | 0.58 |
| Urea Nitrogen (mg/dL) | 10-50 | 44 | 61 | 78 | 78 | 60 | 45 |
| Hemoglobin (g/dL) | 12-16 | 11.2 | 11.0 | 11.0 | 9.2 | 9.3 | 8.9 |
| Hematocrit (%) | 35-47 | 33.6 | 32.3 | 33.2 | 27.5 | 27.9 | 27.1 |
| Leucocytes/mm³ | 4.000-11.000 | 7.190 | 10.570 | 16.620 | 10.020 | 5.090 | 3.950 |
| Platelets/mm³ | 140.000-240.000 | 243.000 | 257.000 | 235.000 | 81.000 | 81.000 | 134.000 |
| LDH# (U/L) | 240-480 | - | 941 | 954 | 961 | - | 853 |
| CRP* (mg/L) | <3 | - | 186 | 186 | 184 | 102 | 62.3 |
| Arterial pH | 7.37-7.44 | - | 7.512 | 7.481 | 7.462 | 7.457 | 7.458 |
| Arterial $PaO_2$ (mm Hg) | 80-90 | - | 74.3 | 66.9 | 68.7 | 88.3 | 80.2 |
| Bicarbonate (mmol/L) | 20-29 | - | 18 | 15.8 | 19.7 | 20.3 | 19.2 |
| Arterial $PaCO_2$ (mm Hg) | 31-42 | - | 22.9 | 21.7 | 41.5 | 29.3 | 19.1 |
| Base Excess (mmol/L) | -3.2 -1.2 | - | -2.8 | -5.2 | -2.6 | -2.3 | -3.1 |
| $PaO_2/FiO_2$ Ratio | >400 | - | 353 | 111 | 114 | 294 | 382 |
| Arterial Lactate (mg/dL) | 4.5-14 | - | 37 | 47 | 28 | 19 | 18 |
| APTT (seconds) | 21-29 | 27.3 | 29.2 | 31 | 30.1 | 31 | - |
| PT (seconds) | 12 | 11.7 | 12.0 | 14 | 14 | 13.5 | - |
| Total Proteins (g/dL) | 6.6-8.7 | 3.7 | 3.6 | 3.8 | - | 3.0 | 3.5 |
| Albumin (g/dL) | 3.4-4.8 | 1.4 | 1.3 | 1.1 | - | 0.9 | 1.0 |
| AST (U/L) | < 31 | 91 | 94 | 87 | 76 | 64 | 124 |
| ALT (U/L) | < 31 | 63 | 60 | 54 | 42 | 40 | 62 |

* CRP: C-reactive protein; # LDH: Lactic dehydrogenase

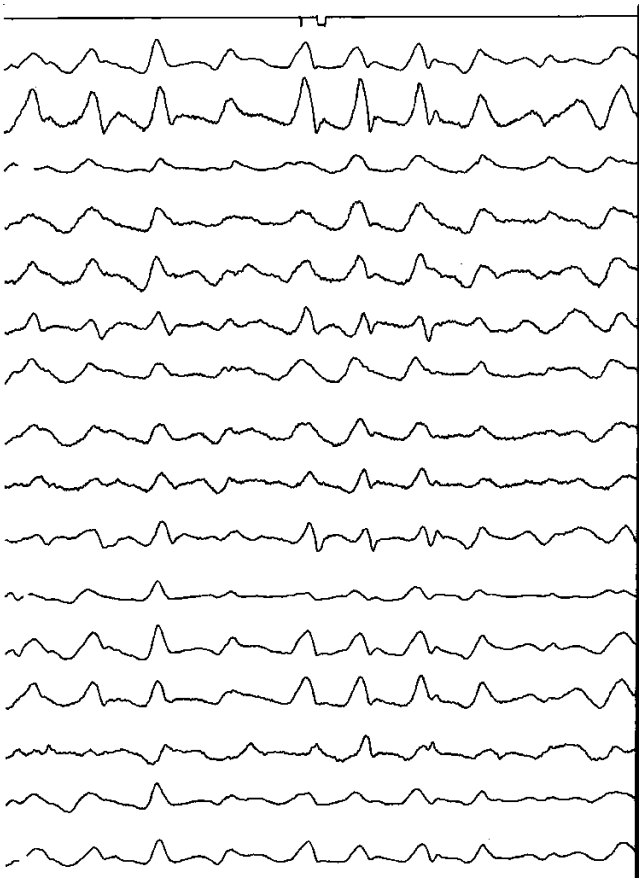

**Figure 1 -** Electroencephalogram pattern showing diffuse cerebral involvement, with slow waves being predominantly delta waves, frequently in a triphasic pattern, mainly at front and sides

ing *Citrobacter freundii* (90%) and *Klebsiella pneumoniae* (10%), both cefepime sensitive; and a blood culture identified a coagulase-negative *Staphylococcus.* Oxacillin was introduced, and clindamycin was interrupted. The absence of remaining placenta was revealed by pelvic ultrasonography; however, there was mild ascites.

**Day 7,** The GCS was 9T (BER = 3, BMR = 5, BVR = 1, and T = orotracheal intubation), and ventilator weaning was initiated.

**Day 8.** Mechanical ventilation was successfully discontinued, and GCS was 11 (BER = 4, BMR = 6, BVR = 1).

**Day 11.** The patient's mental status improved and she was discharged from the intensive care unit. Her neurological physical examination was normal.

**After discharge from the intensive care unit.** A kidney biopsy and histopathology were performed revealing membrano-proliferative glomerulonephritis type III; immunofluorescence was positive for IgM and C3 after treatment with antiprotein serums. The histopathology and immunofluorescence findings were suggestive of nephropathy secondary to schistosomiasis.

## DISCUSSION

This patient with altered mental status was promptly investigated for possible differential diagnoses. First, an acute ischemic stroke or central venous thrombosis were the main diagnostic hypothesis based on her hypercoagulability state (nephrotic syndrome and pregnancy). Nevertheless, the angioresonance results were normal. As shown in the report and laboratory results tables, we also ruled out other differential diagnoses, such as hypoglycemia, hepatic encephalopathy, uremic encephalopathy, electrolyte abnormalities, and central nervous infection.

Preeclampsia was ruled out because the patient presented normal blood pressure during the hospitalization period, and the proteinuria was confirmed to be due to nephropathy secondary to schistosomiasis.

The HELLP syndrome was also ruled out, since hemolysis was not observed (mainly because schizocytes were not found). Neither were low platelets or liver enzymes higher than 3 times the upper limit normality found.

The electroencephalogram (EEG) was indicative of metabolic encephalopathy; there were clinical and laboratory manifestations of sepsis, and antimicrobial therapy produced positive results, all supporting a diagnosis of SAE. The tachycardia and leucocytosis observed on day 2 confirmed the sepsis diagnosis, which was compatible with reports in the literature of SAE preceding sepsis signs.[2] The concomitant recovery from neurologic deficits and improvement of leucocytes, C-reactive protein, and arterial lactate was observed after antimicrobial therapy.

Sepsis-associated encephalopathy can be classified as "early" or "late," with the latter associated with multiorgan failure, while the early form occurs before multiorgan failure develops.[3] The clinical features include altered mental status, fluctuating confusional state, inappropriate behavior, inattention, agitation, delirium, unresponsiveness, coma, paratonic rigidity, and peripheral nerve dysfunction. Less commonly seen are asterixis, cranial nerve dysfunction, myoclonus, lateralization, tremor, and seizures.[3] Most patients who survive present neurological improvement, on average after 5 days, with a range of 2 to 10 days.[4]

Diagnosis of SAE is dependent on the exclusion of other possible causes of brain dysfunction. The EEG is the most sensitive test for SAE, even before clinical findings. A study[5] identified 5 classes of progressively worsened EEG patterns related to worsening outcome: 1 = normal EEG, 2 = excessive theta, 3 = predominant delta, 4 = triphasic waves, 5 = suppression or burst suppression, in ascending order of severity. Cerebrospinal fluid analysis is generally normal or with mild protein elevation.

The pathophysiology of SAE is still incompletely understood; it seems to be multifactorial and not due to direct infection of the central nervous system or to the presence of toxins. It involves inflammatory mediators or response of the brain cells to these mediators. Several studies with animal models or human necropsies have shown cerebral abnormalities, such as ischemic lesions, disseminated microinfarcts, peri-microvessel edema, brain purpura, central pontine myelinolysis, and multifocal necrotizing leucoencephalopathy.[6] Septis-associated encephalopathy seems to be a result of reduced cerebral blood flow and oxygen extraction by the brain, cerebral edema, and disruption of the bloodbrain barrier that may arise from the action of inflammatory mediators on the cerebrovascular endothelium, abnormal neurotransmitter composition of the reticular activating system, impaired astrocyte function, and neuronal degeneration by apoptosis.[7]

This is the first report of a pregnant woman with SAE. In cases classified as early, the neurologic symptoms may be more evident than the signs of sepsis; therefore, SAE should be considered in the differential diagnosis. The presence and severity of SAE correlates with mortality.[1,3] Currently, a specific treatment for SAE does not exist, and a positive neurologic outcome is dependent upon the adequate treatment of sepsis.

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