Typhoid encephalopathy as a neuropsychiatric manifestation of salmonellosis☆

Encefalopatía tifoidea como manifestación neuropsiquiátrica de salmonelosis

A 78-year-old man, with a past history of type 2 diabetes mellitus and high blood pressure, arrived at the emergency room. He had presented with 10 diarrheic bowel movements (Bristol Stool Scale 7) 48 h earlier, nausea, and general weakness. He stated that he had no fever, had not ingested raw or contaminated food, and had no blood or mucus in his stools. In addition, 36 h earlier, he had 2 episodes of vomiting and disorientation, prompting him to seek medical attention at the emergency department. Physical examination revealed low blood pressure (90/60 mmHg), no tachycardia, dehydrated mucous membranes, and no cardiopulmonary alterations. The patient had generalized abdominal pain of 5/10 on the visual analogue scale (VAS) and no signs of peritoneal irritation. The initial neurologic examination detected somnolence and no signs of meningeal irritation. The laboratory work-up reported hemoglobin 11.6 g/dl; MCV 95.5; MCH 31; leukocytes 12,600 cell/mm^3, with neutrophils 10,800 cell/mm^3 and lymphocytes 700 cell/mm^3; platelets 193,000 cell/mm^3; creatinine 1.9 mg/dl (GFR CKD-EPI 33 ml/min/1.73 m^2); urea 113.4 mg/dl; sodium 132.57 mEq/l; potassium 4.52 mEq/l; chloride 105.4 mEq/l; albumin 3.7 g/dl; normal anion GAP metabolic acidosis with pH of 7.25; HCO_3 17.8 mEq/l; PCO_2 42 mmHg; PO_2 45 mmHg; base excess −8.4; and lactate 0.9 mmol/l. The rest of the complete blood count and biochemical profile values were within normal limits. Thyroid profile, coagulation times, ammonia level, and electrocardiogram were also ordered, and all were within normal values. The patient was admitted to the hospital, hydrated with Hartmann solution at 125 cc/h and given supportive care, with neurologic surveillance. During the first 2 days of hospitalization, he presented with fever of 38.7 °C, psychomotor agitation, and disorientation affecting the 3 spheres. The second neurologic examination, conducted 48 h after hospital admission, revealed delirium mixed with somnolence and alternating with periods of agitation, incoherent verbalization, a doubtful plantar response, and no meningism. Given his altered state, the neurologic examination was complemented 24 h later, finding: normal cranial nerve pairs, normal deep tendon reflexes, and indifferent plantar response. Due to the patient's neurologic decline, a non-contrasted tomography scan of the brain and a lumbar puncture were carried out, the results of which were within normal parameters. An electroencephalogram was ordered, reporting: abnormal alertness and mild diffuse cortical dysfunction with triphasic waves, characteristic of encephalopathy, correlating with the clinical data. Cerebrospinal fluid culture was ordered, along with stool panel, gastrointestinal panel PCR, and stool and blood cultures. Continuing management included a decrease in fluids to 80 cc/h. After the cultures were taken, broad-spectrum antibiotic therapy was started with a carbapenem (ertapenem 1 g IV every 24 h). The results of the stool culture reported signs of inflammatory diarrhea, with more than 100 leukocytes per field and positive fecal occult blood. The cerebrospinal fluid and blood cultures were negative, *Salmonella* was detected through PCR testing, and the stool culture was positive for *Salmonella* spp. The antibiogram reported susceptibility to trimethoprim/sulfamethoxazole, ceftriaxone, and ampicillin. Antibiotic therapy was de-escalated to ceftriaxone, combined with azithromycin, and the regimen was completed with a macrolide for 10 days. Twenty-four hours after the first dose of the antibiotic treatment, the patient presented with improvement of the gastrointestinal and neurologic symptoms. On hospitalization day 5, a new neurologic examination revealed a conscious patient, oriented in the 3 spheres, with coherent speech, no agitation, no focal neurologic signs, normal deep tendon reflexes, improved sleep/wake cycle, and only 2-3 bowel movements per day (Bristol Stool scale 5). Control laboratory tests reported improved kidney function, with creatine of 1.1 mg/dl (GFR CKD-EPI 64 ml/min/1.73 m^2), and a new gasometry with pH 7.35, HCO_3 22 mEq/l, PCO_2 41 mmHg, PO_2 29 mmHg, base excess −2.8, and lactate 0.8 mmol/l. On hospitalization day 7, the patient had complete symptom resolution and was discharged with no symptoms on day 10. There are approximately 70,000 cases per year of salmonellosis in Mexico.[1] The present case was one of a rare extraintestinal manifestation (neuropsychiatric) of salmonellosis (typhoid encephalopathy), considering the large number of patients with a *Salmonella*-induced infection in Mexico.[2] As a reference of this presentation in the Americas, specifically in the United States, the neuropsychiatric manifestation of delirium is documented in less than 5% of patients with salmonellosis.[3] The clinical picture of typhoid encephalopathy is characterized by a clinical spectrum of neurologic manifestations that include an altered state of alertness, delirium, confusion, convulsions, and coma, as described by Martin in 1994. Delirium is the main event and presents in 23 to 57% of patients with that diagnosis.[4] The rule-out diagnosis should document an altered state of alertness, convulsions, or delirium, with no associated systemic disease, as well as microbiologic detection of *Salmonella* and the absence of infection in the central nervous system (CNS).[5] The present case was a diagnostic challenge. Given the patient's neurologic decline, a neuroinfection was initially ruled out. The findings of *Salmonella* in the gastrointestinal PCR test, the inflammatory diarrhea, and the results of the electroencephalogram led to our suspicion of the disease. In addition to being a difficult diagnosis, the fact that it was a rule-out diagnosis meant it had to made quickly, requiring a high level of suspicion. Advanced age, leukopenia, a Widal reaction $\geq$ 1:640, and dehydration are independent risk factors for poor prognosis.[6] Our patient had several of those factors, thus treatment had to be started as quickly as possible, as was the case. Treatment is with antibiotic therapy, and high-dose glucocorticoids can be used as coadjuvant therapy in severe cases. The mortality rate is approximately 50% but adequate antibiotic management and the use of dexamethasone can reduce said rate to 13% in severe cases.[7]

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In Mexico in 2014, Vázquez-Garcidueñas reported resistance to ampicillin, carbenicillin, and cephalothin.[8] Empiric antibiotic management is indicated with third-generation cephalosporines or carbapenems. Quinolones are not indicated as empiric management due to their high resistance rate.[9] Supportive care with fluids and the correct application and de-escalation of antibiotics were essential for preventing progression to a more severe form in our patient, thus avoiding the use of glucocorticoids. The antibiogram reported susceptibility to ceftriaxone, and so antibiotic therapy was de-escalated to ceftriaxone 2 g iv/every 24 h, in combination with azithromycin. The double regimen was indicated because of the delayed response to azithromycin, compared with ceftriaxone, and to ensure intravenous administration for at least 7 days.[10] Due to the patient's good response on day 7, the regimen was switched to oral azithromycin for 10 days (500 mg vo/every 24 h). The case presented herein is rare in our clinical practice, and so we consider reporting it important, to aid in the future diagnosis and opportune treatment of such cases.

Ethical considerations

The authors declare that no experiments were conducted on animals or humans in the present research and the protocols of their work centers were followed, with respect to the publication of patient data, preserving patient anonymity at all times.

They also declare that this article contains no information that could identify the patient, thus informed consent on the part of the patient was not required.

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