Salmonella Encephalopathy Treated with Early Use of Intravenous Immunoglobulin and Dexamethasone

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Salmonella encephalopathy is an infrequently reported septic encephalopathy characterized by gastrointestinal manifestations (including fever, vomiting, diarrhea, and abdominal pain), due to non-typhoidal *Salmonella* infection. It is often accompanied by altered consciousness, seizures, or other neurologic symptoms. The pathophysiology of septic encephalopathy has not yet been well established; however, some recent reports reveal that the levels of cytokines, such as interferon gamma, tumor necrosis factor-alpha, and interleukins 6, 8, and 10, in blood and the central nervous system (CNS) are elevated in patients diagnosed with this disease [1]. Several intravenous antibiotics have been used for the empirical treatment of patients suspected of having *Salmonella* encephalopathy, but these have not enabled successful and complete recovery. Ichikawa et al. [1] reported that high-dose methylprednisolone could be used for treating patients with *Salmonella* encephalopathy, without any systemic and neurologic sequelae. We encountered a case of a 15-year-old boy diagnosed with *Salmonella* encephalopathy, who was successfully treated using intravenous immunoglobulin (IVIG) and dexamethasone in addition to empirical antibiotics.

Written informed consent by the patients was waived due to a retrospective nature of our study. A 15-year-old boy who had been previously

healthy visited the emergency department with a 5-day history of fever, and a 3-day history of periumbilical pain, vomiting, diarrhea, and headache. He had eaten soy sauce-marinated fresh crabs continuously for 2 weeks before hospitalization. During those 2 weeks, he sometimes presented abdominal pain, nausea, and diarrhea those were wax and wane. Since 5 days before hospitalization, his symptoms had aggravated gradually. After 13 hours of hospitalization, he developed confusion, drowsiness, generalized tonic seizures, and psychiatric symptoms such as a change in character and inappropriate verbal communication. His body temperature was 39.1°C, blood pressure was 127/58 mm Hg, heart rate was 110/min, and respiratory rate was 20/min. A physical examination revealed a mildly distended abdomen and periumbilical direct tenderness without rebound tenderness. The initial neurologic examination, revealed isochoric pupils with a normal light reflex, full extraocular movement in both eyes, normal motor/sensory function, normal deep tendon reflex, and positive meningeal irritation sign, including neck stiffness, Brudzinski's and Kernig sign. His laboratory findings were as follows: white blood cell (WBC) count, 15,600/ μ L; hemoglobin, 15.3 g/dL; platelet count, 296,000/ μ L; C-reactive protein level, 2.15 mg/dL; erythrocyte sedimenta-

tion rate, 58 mm/hr; high-sensitivity troponin-I level, 732 pg/mL; and N-terminal prohormone brain natriuretic peptide (NT-proBNP) level, 928 mg/dL. The results of cerebrospinal fluid (CSF) analysis were as follows: WBC, 405/ μ L (polymorphonuclear leukocytes, 17%; mononuclear cells, 83%); red blood cell count, 49/ μ L; adjusted WBC, 404/ μ L; glucose level, 48 mg/dL; and total protein concentration, 184 mg/dL. His serum glucose was 101 and CSF/serum glucose ratio was 0.47. Polymerase chain reaction (PCR) analyses were conducted to exclude CSF enterovirus, herpes simplex virus types 1, and 2, and a few bacteria including *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Neisseria meningitidis*, Group B *Streptococcus*, and *Listeria monocytogenes*. PCR results in CSF are all negative. Bacterial culture tests using the CSF, blood, and stool also yielded negative results. PCR analysis of his stool showed a positive reaction only for *Salmonella* spp., but not for *Shigella*, *Vibrio*, *Campylobacter*, *Escherichia coli*, *Clostridium*, and *Yersinia*. Brain magnetic resonance imaging (MRI) with diffusion-weighted imaging was taken on the second day after the encephalopathic symptoms began. MRI revealed no abnormal signal in the gray and white matter (Fig. 1). However, overnight video-electroencephalography, revealed diffuse background slow waves with only few focal epileptiform discharges without subclinical/clinical seizures and those were normalized on next day. Electrocardiography revealed a normal sinus rhythm (Fig. 2). Echocar-

diography was performed because of the high levels of NT-proBNP and troponin-I in the laboratory examinations, and it revealed mild coronary ectasia of the left anterior descending artery (4.9 mm; Z-score, 3.2). Other findings, including the ejection fraction,

Fig. 1. T2-weighted magnetic resonance imaging (MRI) showing no abnormal signal on the gray and or white matters.

Fig. 2. Electroencephalography (EEG) showing diffuse background slow waves with few focal epileptiform discharges and following was normalization.

valvular functions, cardiac wall motions, and pericardial effusion, were all normal. He was administered intravenous cefotaxime (6 g/day), vancomycin (2 g/day), acyclovir (30 mg/kg/day for 5 days), immunoglobulin (1 g/kg/day for 2 days), intravenous dexamethasone (0.3 mg/kg/day for 5 days), and intravenous levetiracetam (10 mg/kg/day for 4 days after an initial loading dose of 20 mg/kg). Two days after starting active treatment, the patient could communicate verbally without confusion and agitation. No additional seizures were noted after the initial presentation. He was discharged after 9 days of hospitalization, without any neurologic sequelae or abdominal discomfort. Follow-up echocardiography performed 2 days after discharge revealed normal valvular function and coronary diameters.

Salmonella encephalopathy is a rarely reported disease, which is considered a manifestation of nontyphoidal *Salmonella* enteritis [1]. Arii et al. [2] recommended the diagnostic criteria for *Salmonella* encephalopathy as follows: (1) encephalopathic features, defined as the presence of an altered state of consciousness, altered cognition or personality, or seizures; (2) detection of nontyphoidal *Salmonella* spp. in stool; (3) absence of other viral or bacterial infection associated with CNS abnormalities; and (4) absence of an alternative explanation for the neurologic or systemic disease [2]. In our patient, the result of the CSF bacterial culture test was negative; however, pleocytosis (WBC, 405/ μ L) and increased protein concentration (184 mg/dL) were noted in the CSF. The findings were highly suspicious of the possibility of bacterial encephalitis. Moreover, the results of the PCR analyses using CSF, stool, and respiratory tract specimens were all negative except *Salmonella* spp. from the stool. The extraneural infection of *Salmonella* without isolation of any viruses or bacteria in the CSF and the systemic manifestations such as cardiac involvement were suggestive that the neurogenic symptoms were systemic manifestation, so called septic encephalopathy due to increased levels of several cytokines or endotoxins [3]. Although we did not examine inflammatory mediators, some reports have shown that cytokines or endotoxins may play important roles in *Salmonella* encephalopathy [1]. Regarding prognosis, *Salmonella* encephalopathy shows severe neurologic sequelae in most diagnosed patients [2]. However, Ichikawa et al. [1] showed favorable outcomes with high-dose methylprednisolone pulse (30 mg/kg/day for 3 days) and empirical antibiotics. IVIG and steroids are used to treat various immune-mediated disease, including febrile infection-related epilepsy syndrome and autoimmune encephalitis [4,5]. In clinical settings, however, the

decision to use IVIG is often delayed because of delayed diagnosis, which could limit its benefits [5]. We used intravenous dexamethasone and IVIG from treatment initiation. We concluded that the early use of both intravenous dexamethasone and IVIG was helpful in the treatment of *Salmonella* encephalopathy.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contribution

Conceptualization: GHK and SHK. Data curation: GHK. Formal analysis: GHK and JHL. Methodology: GHK and JHL. Project administration: SHK. Visualization: GHK and SHK. Writing-original draft: GHK. Writing-review & editing: GHK, JHL, and SHK.

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