

Cerebrospinal Fluid Cytokines in *Salmonella Urbana* Encephalopathy

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MINAMI, K., YANAGAWA, T., OKUDA, M., SUZUKI, H., TAMURA, A., IZUMI, G. and YOSHIKAWA, N. *Cerebrospinal Fluid Cytokines in *Salmonella Urbana* Encephalopathy*. Tohoku J. Exp. Med., 2004, **203** (2), 129-132 — We present a case report of encephalopathy associated with *Salmonella urbana* infection in a child. A 5-year-old boy was admitted to our clinic with convulsions and coma. Cerebrospinal fluid (CSF) interleukin-6 (IL-6) and IL-8 were elevated at onset and were decreased within normal limit on the fifth day. Residual neurological deficits included severe mental deficits and spastic tetraplegia. High levels of CSF proinflammatory cytokines might be related to central nervous system (CNS) disease activity. Although encephalopathy is a rare complication of non-typhi *Salmonella* infection, it should be borne in mind as an occasionally serious and potentially lethal disease. ——— *Salmonella urbana*; encephalopathy; cytokines

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Salmonellosis is a common human and animal infection. Enterocolitis is the typical disorder caused by *Salmonella* infection (Gomez and Cleary 1998), and central nervous system (CNS) involvement can be a serious complication of non-typhi *Salmonella* infection (Martin et al. 1994; Arii et al. 2002). We report a case of salmonellosis and encephalopathy caused by *Salmonella urbana* infection in a 5-year-old boy.

CASE REPORT

The patient was admitted to Wakayama Medical University with a 33-hour history of fre-

quent watery diarrhea, high fever, and had a episode of tonic-clonic convulsion followed by coma. He had been in good health before this episode and had kept a red-eared turtle as a pet. Physical examinations upon admission showed that he was in a comatose state (a Glasgow Coma Scale score of 6 of 15) with a decorticated posture. His body temperature was 39.0°C, and his blood pressure was 90/60 mmHg. His pupils were 5 mm across, symmetric, and slow to react to light. The deep tendon reflexes were hyperactive and the Babinski sign was negative. The patient's abdomen was distended, but no enlarge-

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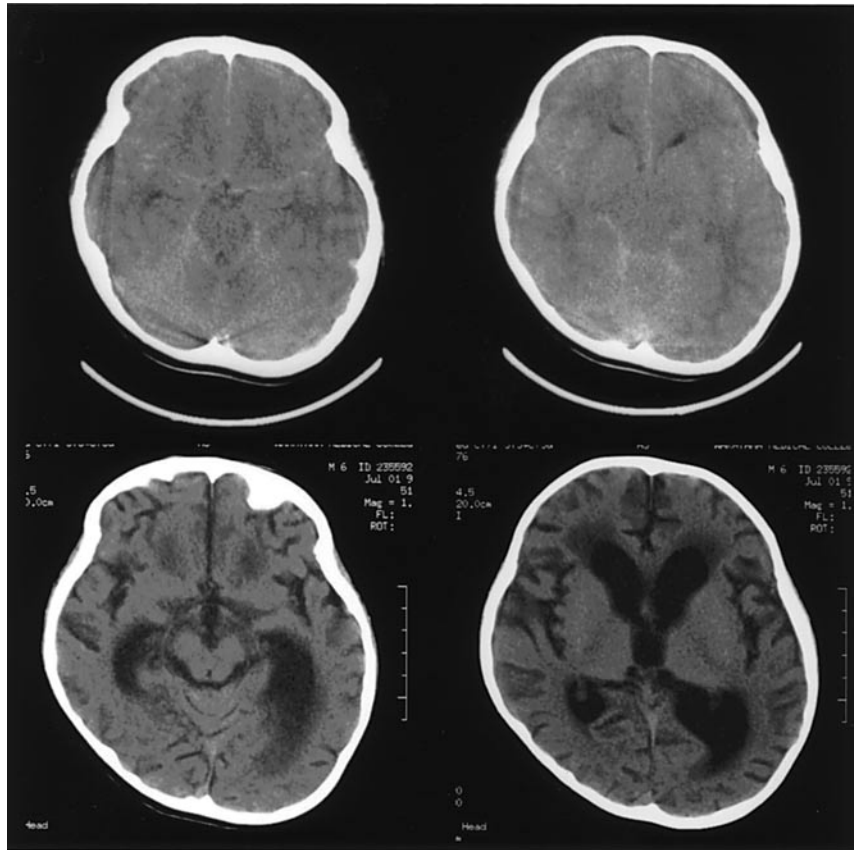


Fig.1. Brain CT scans of the patient with *Salmonella urbana*-associated encephalopathy. *Top*, Image taken on admission, showing brain edema, especially the midbrain and pons. *Bottom*, Image taken on day 52 of hospitalization, showing diffuse brain atrophy.

ment of the liver or spleen was noticed. Laboratory findings were as follows: white blood cell count $4000/\mu\text{l}$ (79% neutrophils, 9% monocytes, and 12% lymphocytes); hemoglobin 14.1 g/100 ml; platelets $152 \times 10^3/\mu\text{l}$; C-reactive protein 23.3 mg/100 ml; Na 129 mmol/liter; K 3.4 mmol/liter; Cl 99 mmol/liter; BUN 36 mg/100 ml; creatinine 0.8 mg/100 ml; AST 46 U/liter; ALT 30 U/liter; LDH 669 U/liter; arterial blood pH 7.435; HCO_3^- 11.6 mmol/liter; base excess -10.5 mmol/liter. Endotoxin was not examined. Blood culture did not show growth of any organism. Cerebrospinal fluid (CSF) analysis revealed a normal cell count (0 cells/ μl), a protein level of 22 mg/100 ml, a glucose concentration of 71 mg/100 ml, and negative bacterial culture. Serum levels of the cytokines interleukin-1beta (IL-1beta), IL-6, IL-8, interferon-gamma (IFN-gamma) and

tumor necrosis factor-alpha (TNF-alpha) measured with the Biotrack ELISA system (Amersham Pharmacia Biotech UK Ltd., Buckinghamshire, UK) were elevated to 19.6 pg/ml (minimum detectable dose; <1.0), 277.5 pg/ml (<1.0), 134.0 pg/ml (<2.0) and 1187.5 pg/ml (<2.0), respectively. TNF-alpha was not detected in the serum. CSF levels of the cytokine IL-6 and IL-8 were elevated to 123.5 pg/ml (<1.0) and 60.3 pg/ml (<2.0). IL-1beta, IFN-gamma and TNF-alpha in CSF were not measured.

Cranial computed tomography (CT) on admission showed severe brain edema, particularly localized to the pons and midbrain (Fig. 1, top). The patient's electroencephalogram showed slow and diffuse high-amplitude waves. The patient required assisted ventilation because his breathing was irregular. Intravenous administration of fos-

fomycin, dexamethasone and mannitol was started. The patient's temperature did not decrease. *Salmonella urbana* was cultured from both his stools and the red-eared turtle he kept as a pet. After change of the antibiotic to aztreonam, his condition improved. He could do an opening-eye posture, could not see, hear, or speak. On the fifth day serum IL-6, IL-8 and IFN-gamma were decreased to 16.8 pg/ml, 15.0 pg/ml and 12.1 pg/ml. CSF IL-6 and IL-8 were decreased to 1.6 pg/ml and 5.3 pg/ml. CT scan on day 52 of hospitalization showed severe brain atrophy (Fig. 1, bottom). The patient was discharged from hospital 120 days after admission with residual severe mental and neurological deficits including spastic tetraplegia.

DISCUSSION

Salmonella infection has been commonly reported in humans and animals (Gomez and Cleary 1998). Most human infections are acquired by eating contaminated food and occasionally by contact with reptilian pets (Sanyal et al. 1997). Individuals develop clinical manifestations such as acute gastroenteritis, bacteremia, enteric fever, and metastatic focal infections, or may be merely asymptomatic carriers. CNS manifestations have been widely reported in relation to enteric fever (Gomez and Cleary 1998). This particular case took a very serious and acute clinical course, resulting in spastic tetraplegia and severe mental retardation. Although an outbreak of *Salmonella urbana* infection has been reported (Sirinavin et al. 1991), encephalopathy is a rare complication of *Salmonella urbana* infection.

The pathophysiology of encephalopathy associated with *Salmonella* infection has not been elucidated. In some cases, severe dehydration or electrolyte imbalances cause *Salmonella* encephalopathy. However, the clinical and laboratory evidence in this case was inconsistent with the assumption that the encephalopathy was caused by only dehydration or electrolyte imbalance. Both blood and CSF cultures were found to be negative. This reflects that the infecting organism is

not the direct cause of the encephalopathy. Serum levels of IL-1beta, IL-6, IL-8 and IFN-gamma were markedly elevated. CSF levels of IL-6, IL-8 were also elevated. The result of the serum TNF-alpha test was unclear. We suggest that sample collection time may play an important role in detection of TNF- α . The serum TNF- α concentration was highest at 3.6 hours after the injection of *Salmonella minnesota* endotoxin and was not detected by 24 hours (Silva et al. 1993). Their result also supports our findings. Serum cytokine levels in *Salmonella* enterocolitis are generally much lower than those seen in this case (unpublished data). In this state of encephalopathy these data reflect a systemic release of inflammatory mediators such as the hypercytokinemia. These results suggest that *Salmonella* encephalopathy might be a consequence of systemic immune responses associated with some cytotoxic etiology.

The role of cytokines in the pathogenesis of encephalopathy is still unknown. A single large injection of *Salmonella* endotoxin caused a syndrome of shock and organ injury (Silva et al. 1993). Various bacterial products other than endotoxin from *Salmonella* have been proposed as potent inducers of cytokine expression by immune cell (Jones 1997). Proinflammatory cytokine mRNAs in the brain, especially in the choroid plexus, the circumventricular organs, and meninges were induced after peripheral injections of bacterial lipopolysaccharide (LPS) (Quan et al. 1999). IL-6 is secreted from human brain endothelial cells by exposure of IL-1beta, or LPS or an oxidative challenge (hypoxia) and is known to have neurotrophic and neuroprotective functions (Reyes et al. 1999). On the other hand, it was reported that transgenic mice with cerebral overexpression of IL-6 developed severe neurologic disease (Campbell et al. 1993). Although the CSF levels of cytokines are elevated in some patients with acute encephalitis or encephalopathy (Ichiyama et al. 1998), there have been no studies about CSF cytokines in *Salmonella* encephalopathy in the English language literature.

The blood-brain barrier (BBB), which nor-

mally maintains a homeostatic environment for brain cells, acts as an immune response modifier within the CNS. The brain microvessel endothelial cells forming the BBB are affected by a number of different pro-inflammatory mediators such as cytokines. These cytokines play an important role in initiating the changes in the permeability of the brain endothelial cells, and in releasing secondary immune response modulators from the BBB. The accumulation of cytokines progresses in the CNS and results in "cytokine storm" in the brain, and then brain edema and the degenerative changes in the neural cells occur (Miller 1999). Several inflammatory cytokines-induced breakdown of the BBB and neurotoxicity are suggested to be possible causes of influenza-associated encephalopathy (Yokota et al. 2000). CSF cytokines activity in the present case was increased when *Salmonella* encephalopathy showed active CNS disease and decreased when CNS manifestations were improved. The high CSF concentrations of IL-6 and IL-8 might be associated with progression to encephalopathy. It will be necessary to further investigate the factors contributing to *Salmonella* encephalopathy.

Although encephalopathy is a rare complication of non-typhi *Salmonella* infection, it should be borne in mind as an occasionally serious and potentially lethal disease.

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