J Tokyo Wom Med Univ
70(Ext) E106~E112 (2000)

A Case of Acute Encephalopathy Following *Salmonella enteritidis* Gastroenteritis

Mihoko MATSUZAKI, Yukiko HIRANO and Makiko OSAWA
Department of Pediatrics (Director: Prof. Makiko OSAWA)
Tokyo Women's Medical University, School of Medicine
(Received, Feb. 18, 2000)

A 3-year-old boy who presented with prodomal *Salmonella* (*S.*) *enteritidis* (O : 9 H : G) followed by acute encephalopathy prior to transient mild renal impairment due to intravascular consumptive microcoagulopathy is described.

Introduction

Salmonella is prevalent throughout the world, and is a more common enteric pathogen than is generally recognized. Salmonella species can cause a broad spectrum of disorders ranging from overt gastroenteritis to enteric fever and bacteremia as well as asymptomatic carrier status[1]. Central nervous system (CNS) infection is a rare manifestation of non-typhoidal Salmonellosis, and may involve meningitis[2], brain abscess, subdural empyema[3] or encephalopathy[4)~6)]. We report a recent case of encephalopathy associated with *Salmonella* (*S.*) *enteritidis* infection following acute gastroenteritis, in whom the CNS manifestations were presumed to be toxin-related.

Case Report

The patient was a 3-year 3-month-old boy who had been born at term weighing 2,285 g, without asphyxia, and had shown normal developmental milestones. There was no evidence of immune system suppression or dysfunction. He experienced a simple febrile convulsion at 2-years 9-months of age. His maternal uncle also had a history of febrile convulsions in childhood.

The patient had acute gastroenteritis with fever for 4 days, vomiting and frequent musty-smelling watery, bloody diarrhea with crampy abdominal pain (40 times/day at a maximum). The symptoms subsided on the 11th day of illness with conservative therapy, but without antimicrobial therapy. Stool culture revealed *S. enteritidis* (O : 9 H : G). On the 12th day, his fever again rose to 39 ℃ with cough and rhinorrhea. On the 13th day he had frequent vomiting and had a generalized tonic clonic convulsion that lasted 3 minutes, and was admitted to our department.

He was a slender boy, 99.0 cm (+0.86 SD) in height and weighing 11.9 kg (−1.53 SD). The physical examination revealed stupor, consciousness score 9 (eyes 2, motor 5, verbal 2) on the Glasgow coma scale, a body temperature of 38.2 ℃, heart rate 144/min, respiratory rate 42 breaths/min, blood pressure 98/58 mmHg and no skin rash. Consciousness shifted from stupor to somnolence (score 12: eyes 3, motor 5, verbal 4) without nuchal rigidity.

Initial laboratory investigations revealed leucocytosis of 24,500 cells/μl (neutrocytes 69.5%, lymphocytes 27.0%) and C-reactive protein 5.6 mg/dl. Other laboratory investigations including uri-

nalysis, serum chemistry, serum ammonia, blood gas analysis, serum lactate and pyruvate, and chest and abdominal roentgenograms yielded normal findings. A lumbar puncture revealed a cerebral spinal fluid pressure of 280 mmH_20; there were 2 neutrocytes and 5 lymphocytes per 3 μl, and the IgG index was 0.50. We diagnosed sepsis and acute encephalopathy associated with prolonged consciousness loss of more than 72 hours, and broad spectrum antibiotics were administered. Seizures were easily controlled with conventional doses of diazepam suppositories (0.5 mg/kg, twice).

He had spiking fevers, up to 42 ℃, from the 13-th day, and was oliguric with cylinduria and proteinuria on the 14th day. Diarrhea reappeared on the 15th day. Thrombocytopenia (platelet count 60,000 /μl), and anemia (Hb 9.7 g/dl) without evidence of red-cell fragmentation were also manifest. APTT was 44.1 sec (control 29.9 sec), β_2 microglobulin in urine was 1,300 μg/dl. The diagnosis was either hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP). Renal dysfunction was mild and transient, such that dialysis was not required.

On the 15th day the position of the eyes at rest deviated to the upper left position, he had spontaneous eye movements, and corneal reflex and light reaction were brisk. Doll's eye manoeuvre was positive, suggesting that the brainstem was not involved. No pinpoint pupils or papilloedema were seen. His facial appearance was symmetric, and gag reflex was positive. Muscle power in all four limbs was maintained, and muscle tone was hypertonic. Deep tendon reflexes were exaggerated, and Babinski reflex and patellar clonus were bilateral. Motor response to noxious stimulation was decorticate posture. Extrapyramidal signs such as dystonia and dyskinesia were not apparent. On the 19th day spontaneous movement and speech were diminished, and emotional

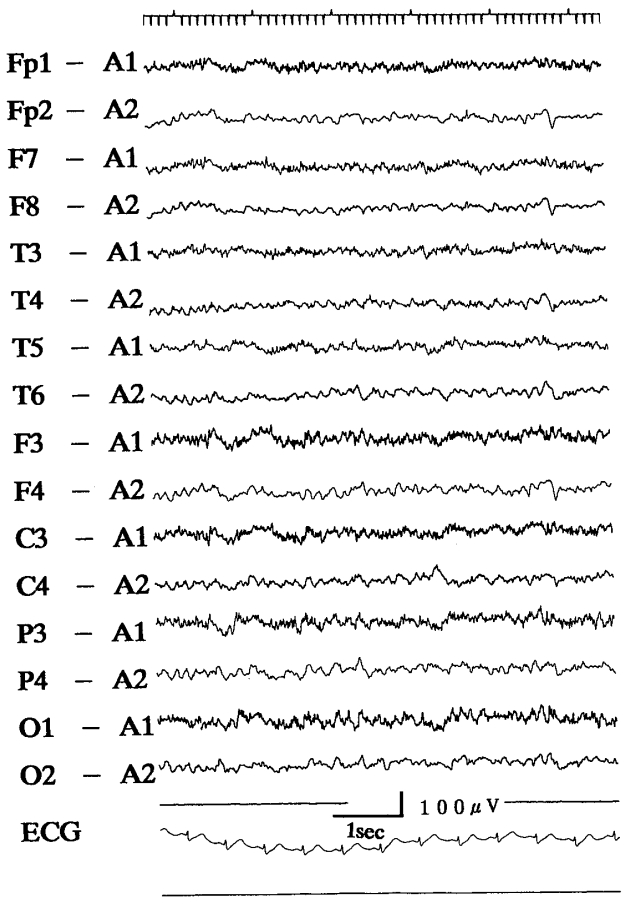

Fig. 1 EEG showed 5～8 Hz slow waves predominantly in the right occipital area on the 16th day.

incontinence, grasp reflex and sucking reflex were seen.

Repeat stool culture revealed *S. enteritidis* (O : 9 H : G). Therefore intravenous fosfomycin was commenced. The cultures of both blood and CSF were negative for bacteria. Blood was assayed for endotoxin using an endotoxin-specific chromogenic Limulus test (Endospecy test, Seikagaku Co., Tokyo, Japan) and plasma was pretreated by the new perchloric acid method. The result was negative.

EEG exhibited 5～8 Hz slow waves predominantly in the right occipital area on the 16th day (3 days after the convulsion) (Fig. 1). Predominant EEG activity became slower, diffuse 2.5～7 Hz slow waves without eileptiform discharges on the 19th day (Fig. 2), consistent with encephalo-

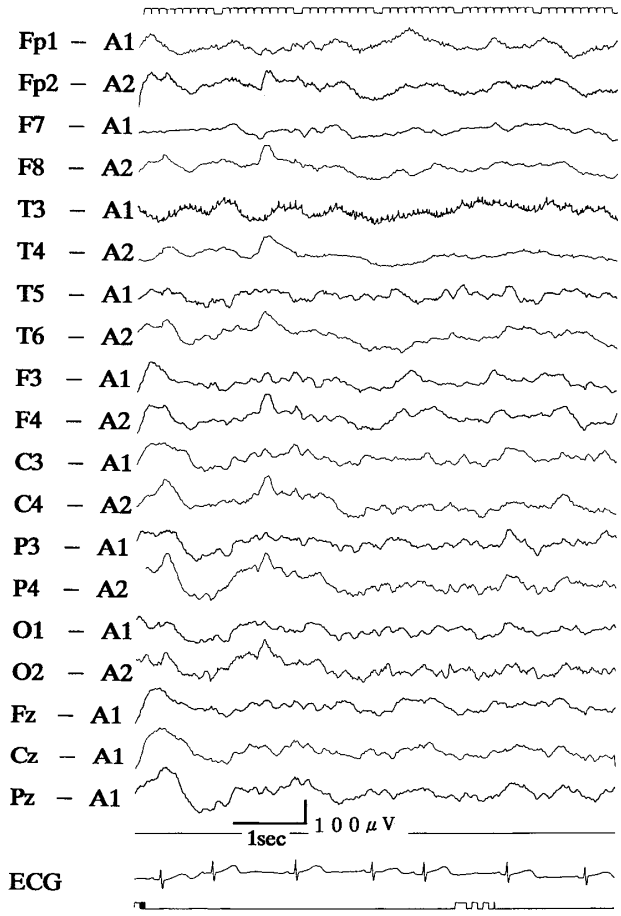

Fig. 2 EEG showed 2.5～7 Hz slow waves on the 19th day.

pathy.

On the 19th day, brain magnetic resonance imaging (MRI) demonstrated generalized brain edema, but no infarctions or massive organic lesions (Fig. 3, left). However, on the 52nd day, MRI revealed moderate frontal and temporal diffuse brain atrophy (Fig. 3, right), and single photon emission computed tomography (SPECT) revealed hypoperfusion in bilateral frontal regions, suggesting regional flow differences.

He could sit alone on the 29th day, and could walk unaided on the 44th day. He spoke monosyllabic nonsense on the 57th day, and a few single words in the 5th month. Speech developmental milestones corresponded to an age of 1 year 9 months. Moderate psychomotor impairment persisted, and speech was more affected than motor

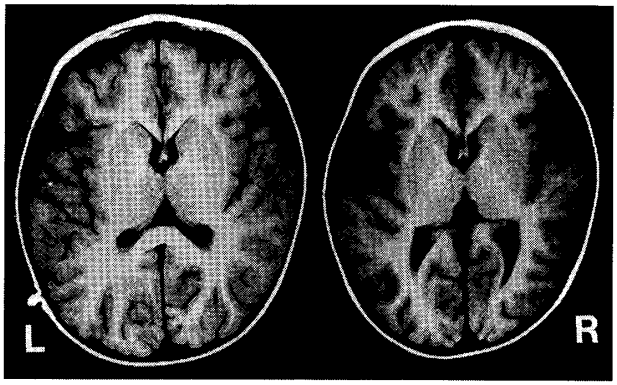

Fig. 3 MRI revealed generalized brain edema on the 19th day (left) and moderate frontal and temporal diffuse brain atrophy on the 52nd day (right).

function. He continued to shed *S. enteritidis* in the stool for 9 months after recovery.

Discussion

Neuro-psychiatric complications are uncommon in non-typhoidal Salmonella infection. The important features of our case included: (1) prodromal gastroenteritis associated with painful defecation; (2) a sustained fever spiking up to 42 ℃, suggesting enteric infection; (3) seizure and loss of consciousness that occurred in the absence of uremia and hypertension, indicating that the CNS was the primary target site prior to mild renal impairment; (4) exacerbation of gastroenteritis after the CNS manifestations, possibly reflecting increased susceptibility to Salmonella infection; and (5) transient mild renal tubular dysfunction with intravascular consumptive microcoagulopathy. Despite this latter renal dysfunction, our case did not manifest the full triad of HUS[7], i. e. microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure[8], or symtoms of TTP. TTP represents a clinical spectrum arising from the same underlying disease process as HUS, but differs mainly in the distribution of thrombotic lesions[9], age of onset, and in the fact that neurological signs and fever are more prominent in TTP[10]. Most cases of TTP present without any antecedent illness, whereas a prodomal

diarrheal illness is an essential feature of classical HUS[10]. HUS most frequently follows gastroenteritis caused by the enteropathogenic *Escherichia coli* (EC) strain O157: H7, *Shigella, Salmonella, Campylobacter, Streptococcus pneumoniae* or viral infections with endotoxemia[7].

The causative agent in our case was *S. enteritidis*, which has become one of the most common serotypes among non-typhoidal Salmonella infections in recent years. It is likely that, since lipopolysaccharide (LPS) was not detected in our patient's blood, endotoxemia had occurred early in the disease course. We were unable to identify the toxin acting on the CNS and kidney in this case. Controversy persists as to whether a direct vascular insult due to LPS, or the actions of LPS mediators on the CNS are responsible for neurotoxicity. Other toxins, produced by as yet unknown mechanisms, may also participate in the pathogenesis of this agent.

Salmonella may multiply, penetrate the epithelium and invade Peyer's patches. The clinical symptoms depend on the production of an endotoxin[1], which is a complex LPS that constitutes the outer portion of the cell wall of all gram-negative rods. The prominent pathophysiological responses to this LPS are fever, shock and disseminated intravascular coagulation[11].

Upon entry of LPS into the circulation from the intestine, LPS rapidly binds to serum protein, and these complexes stimulate endothelial cells, neutrophils, and monocytes. Multiple profound effects are exerted on macrophages, mononuclear cells, lymphocytes, platelets and endothelial cells, which may release inflammatory cytokines and nitric oxide. The lethal effects of LPS may be exerted via tumor necrosis factor-α (TNF-α)[11]. Excess secretion of TNF-α causes endotoxic shock[12]. These endotoxin mediated effects include cytotoxic and systemic inflammatory responses, multiple organ failure and endotoxic shock[11].

LPS causes renal glomerular changes in rabbits. Endothelial damage followed by leucocyte and platelet infiltration into glomerular capillaries suggests that inflammatory cells play a role in the development of microvascular thrombosis, such that there appears to be a close relationship between LPS and HUS[13]. The renal lesions in HUS may include glomerular thrombotic microangiopathy (TMA), cortical necrosis and arterial TMA[14].

Several mechanisms have been proposed to explain the CNS manifestations that accompany HUS. Upadhyaya et al[15] reported that focal areas of infarction with surrounding edema and necrosis in the cerebral cortex and basal ganglion could be the result of widespread microthrombi, and that the extent and severity of non-renal involvement are important determinants of ultimate prognosis[15]. It is also noteworthy that CNS complications are the most frequent cause of death[16].

Some CNS signs of HUS might be attributable to renal dysfunction leading to hypertension, uremia and other metabolic abnormalities[17]. However, in our case, CNS involvement preceded the mild renal dysfunction, suggesting primary CNS involvement caused by a neurotoxin. Cimolai et al[18] reported that CNS involvement was not associated with the risk factors azotemia, hyponatremia or hypocalcemia.

Neurological complications are an important predictive factor for HUS mortality in children[15]. CNS involvement including generalized or focal seizures, coma, paralysis, hemiparesis, decerebrate posturing, alterations in personality and consciousness and blindness have variously been reported as complications in 18/117 (15%)[19], 32/147 (22%)[20], 5/15 (33%)[15], 15/44 (34%)[21] and 30/61 (48%)[17] patients with HUS, respectively. These complications can also reflect cerebral vascular lesions with infarct and hemorrhage[22].

EEG abnormalities such as diffuse slowing without focality and epileptic focal discharges are consistently found in patients with HUS complicated by seizures[23]. Neuroimaging results vary from normal to cerebral edema and hemorrhagic infarction of the basal ganglia, thalamus, hippocampus and cortex on computerized tomography and MRI[22][23], as well as reduced cerebral perfusion on SPECT[24].

Acute encephalopathy is not a single disease entity. Animal models that use verotoxin (VT; at least two serologically different toxins, VT1 and VT2 have been implicated in human disease) have been used to study the pathogenesis of acute encephalopathy associated with HUS. Neurotoxins cause neurological damage because of their effects on endothelial cells of the small vessels suppling neurons[25], and via a direct effect on the nerve cells[26]in the absence of renal impairment in rabbits. Circulating VT2 causes microvascular endothelial cell damage in susceptible target cells such as the spinal cord, brain, cecum, colon, and small bowel. Either intravenous or intrathecal VT2 can lead to primary vascular damage, and produce leaky capillary syndrome, vessel wall dysfunction, edema, and hemorrhage, even in the absence of thrombosis in the CNS and gastrointestinal tract. Pathological examination of the CNS revealed two lesion types; neurons in various CNS regions showed atrophy, cytoplasmic hyperchromasia and nuclear pyknosis as early as 6 hours after administration of VT2, while late vascular changes such as thickening of arteriolar walls, thrombosis and multiple infarctions were noted from 2 days after administration. Both types of change might have been due to VT2 that had invaded the CNS by crossing or circumventing the blood brain barrier. VT2 disappeared rapidly from the blood after intravenous administration, with specific high accumulation in the CNS and gastrointestinal tissues within 24 hours[26].

It is assumed that organ damage requires the presence of VT1 receptors on the red blood cell membrane[27] and the surfaces of vascular endothelial cells. Symptoms of the disease might depend on the distribution of specific VT1 receptors[28]. Lingwood et al[27] demonstrated that glycolipid globotriosyl ceramide (Gb3), a major component of glycolipids in the human renal cortex and medulla, was the functional binding receptor for VT1. Erythrocytes contain VT1 receptors, which might have structural similarities to Gb3, and therefore damaged and fragmented erythrocytes are removed by the reticuloendothelial system following mechanical injury[10]. Following receptor binding, VT1 is internalized by a specific receptor-mediated endocytic event.

Plasma exchange and gammaglobulin might be effective treatments for the neutralization of endotoxin via an antibody which protects against the biological effects of the toxin. The inhibition of cytokine production, or anticytokine therapy, might also be effective. Therapy aimed at improving cerebral blood flow and decreasing the vulnerability of neurons to irreversible ischemic death should also be considered.

References

1) **Singh-Naz N, Rodriguez WJ**: Non-typhoidal Salmonella. In Pediatric Infectious Diseases (Jenson HB, Baltimore RS eds) pp1084–1092, Appleton & Lange, Norwalk (1995)
2) **Henderson LL**: Salmonella meningitis. A.M.A. J Dis Child **75**: 351–375, 1948
3) **Rodriguez RE, Valero V, Watanakunakorn C**: Salmonella focal intracranial infections: review of the world literature (1884—1984) and report of an unusual case. Rev Infect Dis **8**: 31–41, 1986
4) **Zellweger H, Idriss H**: Encephalopathy in Salmonella infections. A.M.A. J Dis Child **99**: 770–777, 1960
5) **Daras M, Blankfein R, Singh BM**: Salmonella choleraesuis encephalopathy. N Y State J Med **80**: 1606–1607, 1980
6) **Martin K, Sharland M, Davies EG**: Encephalopa-

thy associated with Salmonella enteritidis infection. Scand J Infect Dis **26**: 486–488, 1994

7) **Bergstein JM**: Hemolytic-uremic syndrome. *In* Nelson Textbook of Pediatrics 16th ed (Behrman RE, Kliegman RM, Arvin AM et al eds) pp1586–1587, Saunders, Philadelphia (2000)
8) **Gasser VC, Gautier E, Steck A et al**: Hämolytisch-urämische syndrome: Bilaterale Nierenrindennekrosen bei akuten erworbenen hämolytischen Anämien. Schweiz Med Wochenschr **85**: 905–909, 1955
9) **Morrison DM, Tyrrell DL, Jewell LD**: Colonic biopsy in verotoxin-induced hemorrhagic colitis and thrombotic thrombocytopenic purpura (TTP). Am J Clin Pathol **86**: 108–112, 1986
10) **Karmali MA**: Infection by verocytotoxin-producing Escherichia coli. Clin Microbiol Rev **2**: 15–38, 1989
11) **Morrison DC, Ryan JL**: Endotoxins and disease mechanisms. Annu Rev Med **38**: 417–432, 1987
12) **Wright SD, Ramos RA, Tobias PS et al**: CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. Science **249**: 1431–1433, 1990
13) **Bertini T, Abbate M, Zoja C et al**: Sequence of glomerular changes in experimental endotoxemia: a possible model of hemolytic uremic syndrome. Nephron **53**: 330–337, 1989
14) **Habib R, Lévy M, Gagnadoux M et al**: Prognosis of the hemolytic uremic syndrome in children. Adv Nephrol **11**: 99–128, 1982
15) **Upadhyaya K, Barwick K, Fishaut M et al**: The importance of nonrenal involvement in hemolytic-uremic syndrome. Pediatrics **65**: 115–120, 1980
16) **Robson WLM, Leung AKC, Montgomery MD**: Causes of death in hemolytic uremic syndrome. Child Nephrol Urol **11**: 228–233, 1991
17) **Bale JF, Brasher C, Siegler RL**: CNS manifestations of the hemolytic-uremic syndrome. Am J Dis Child **134**: 869–872, 1980
18) **Cimolai N, Morrison BJ, Carter JE**: Risk factors for the central nervous system manifestations of gastroenteritis-associated hemolytic-uremic syndrome. Pediatrics **90**: 616–621, 1992
19) **Martin DL, MacDonald KL, White KE et al**: The epidemiology and clinical aspects of the hemolytic uremic syndrome in Minnesota. N Engl J Med **323**: 1161–1167, 1990
20) **Loirat C, Baudouin V, Sonsino E et al**: Hemolytic-uremic syndrome in the child. Adv Nephrol **22**: 141–168, 1993
21) **Sheth KJ, Swick HM, Haworth N**: Neurological involvement in hemolytic-uremic syndrome. Ann Neurol **19**: 90–93, 1986
22) **Hahn JS, Havens PL, Higgins JJ et al**: Neurological complications of hemolytic-uremic syndrome. J Child Neurol **4**: 108–113, 1989
23) **Dhuna A, Pascual-Leone A, Talwar D et al**: EEG and seizures in children with hemolytic-uremic syndrome. Epilepsia **33**: 482–486, 1992
24) **Fitzpatrick MM, Dillon MJ, Gordon I et al**: Central nervous system involvement in diarrhoea-associated haemolytic uraemic syndrome (D+HUS). Pediatr Nephrol **6**: C166, 1992
25) **Richardson SE, Rotman TA, Jay V et al**: Experimental verocytotoxemia in rabbits. Infect Immun **60**: 4154–4167, 1992
26) **Mizuguchi M, Tanaka S, Fujii I et al**: Neuronal and vascular pathology produced by verocytotoxin 2 in the rabbit central nervous system. Acta Neuropathol **91**: 254–262, 1996
27) **Lingwood CA, Law H, Richardson S et al**: Glycolipid binding of purified and recombinant Escherichia coli produced verotoxin in vitro. J Biol Chem **262**: 8834–8839, 1987
28) **Zoja C, Corna D, Farina C et al**: Verotoxin glycolipid receptors determine the localization of microangiopathic process in rabbits given verotoxin-1. J Lab Clin Med **120**: 229–238, 1992

Salmonella enteritidis 腸炎に合併した急性脳症の1男児例

東京女子医科大学　医学部　小児科学

松崎美保子（マツザキミホコ）・平野　幸子（ヒラノユキコ）・大澤真木子（オオサワマキコ）

易感染性を持たない3歳男児が，非チフス性サルモネラ菌 *Salmonella enteritidis* O：9H：G 感染による腸炎に罹患した．対症療法で6病日に解熱し，最高40回/日におよぶ下痢は11病日にいったん軽快した．12病日に再発熱し，13病日に嘔吐，および全身性強直性間代性けいれん後に意識障害が遷延した．自発言語消失，感情失禁，共同偏視，痙性・膝クローヌスなどの錐体路徴候を認めた．頭部画像は脳浮腫を，脳波は徐波化を，髄液は細胞数増多を伴っていないことより急性脳症と診断した．消化管からサルモネラ排菌は持続したが，血液・髄液培養および血中エンドトキシンは陰性で，サルモネラ菌の中枢神経系への直接侵襲を証明できなかった．急性期に一過性に乏尿が出現し，タンパク尿，円柱尿，尿中 β_2MG の上昇，貧血，血小板減少症，血液凝固能亢進が認められた．サルモネラ感染症は，消化器系，中枢神経系，腎尿細管，血管内血液凝固系に及んだ．消化管から排菌は持続したが，知的精神遅滞を残して回復した．エンドトキシン，サイトカインが症状発現に関与していると推測した．