

## Case Report



# Nontyphoidal *Salmonella* Meningitis in an Immunocompetent Child

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

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## ABSTRACT

*Salmonella* meningitis is rare yet poses causes significant neurological morbidity in children. Infants, especially those under 3 months of age, and those with immunocompromised states, such as malignancy, malaria, and human immunodeficiency virus infection, are at increased risk for developing *Salmonella* meningitis. Herein, we describe a case of *Salmonella* meningitis in a previous healthy 8-year-old girl who presented with high fever, vomiting, and altered mental status. Group D *Salmonella* species were isolated in cerebrospinal fluid culture, and no abnormal findings were noted in brain magnetic resonance imaging. Immunoglobulin levels and lymphocyte subset counts were within the normal ranges, and no genetic mutation responsible for primary immunodeficiency disease was detected by next-generation sequencing. The patient's condition improved rapidly with third-generation cephalosporin, and no complications or sequelae developed. Nontyphoidal *Salmonella* can cause meningitis in immunocompetent children and can be successfully treated with early administration of antibiotics.

**Keywords:** Meningitis; *Salmonella*; Immunocompetence; Child

## INTRODUCTION

*Salmonella* are gram-negative bacilli of the *Enterobacteriaceae* family that are classified into two species: *Salmonella enterica* and *S. bongori*.<sup>1</sup> The *S. enterica* species is subdivided into six subspecies and is further differentiated by serotyping. Based on the immunoreactivity of the O and H antigens, there are more than 2500 designated *Salmonella* serotypes. *Salmonella* organisms can also be simply classified as *Salmonella* associated with enteric fever (*S. enterica* ser. Typhi or *S. ser. Paratyphi*) or nontyphoidal *Salmonella* (NTS) according to the clinical disease.<sup>2</sup>

NTS most commonly causes gastroenteritis in humans via contaminated food or water or contact with infected animals.<sup>2</sup> Infected children manifest with vomiting, abdominal cramps, diarrhea, and fever. Less frequently, bacteremia can occur, especially in children with previous gastrointestinal disease, severe malnutrition, or human immunodeficiency virus (HIV) infection.<sup>1</sup> Focal infections, most commonly in the bones and in the central nervous system, may occur in infants (especially <3 months of age) and in children in an

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immunocompromised state.<sup>3)</sup> Among them, meningitis due to NTS has a high morbidity and long-term neurologic sequelae.<sup>4)</sup> NTS meningitis in children is frequently complicated by seizures, abscesses, hydrocephalus and subdural empyema, and children may have severe developmental delay and motor disabilities.

NTS meningitis in healthy children beyond infancy is known to be rare, and only a few studies have been published. Here, we report the first case of NTS meningitis in an immunocompetent child in South Korea presenting with fever, vomiting and mental disorientation. The clinical course and treatment of the patient is described along with a literature review on *Salmonella* meningitis in children.

## CASE

A previous healthy 8-year-old girl was admitted to the emergency room with a chief complaint of high fever and vomiting. The symptoms started four days prior to admission and were persistent. Additional symptoms included headache and intermittent abdominal pain, and she also had poor oral intake with decreased urination. The patient did not have diarrhea. Since the day before admission, she appeared to be talking to herself at times. The patient had a history of eating clams with her family three days prior to onset of the fever, but denied eating raw milk, poultry, meat or egg products. No other remarkable medical or perinatal history was noted, and other family members were asymptomatic. On initial physical examination, the patient was somnolent, and her blood pressure was 120/72 mmHg, heart rate 121/min, respiratory rate 18/min, and body temperature 39.4°C. Chest and cardiac examinations did not reveal any abnormalities, but her abdomen was tender in the periumbilical area. She had neck stiffness, and Kernig's and Brudzinski's signs were positive. During the stay in the emergency room, the patient's blood pressure rose to 214/113 mmHg; hence, urgent brain CT was performed, and no cerebral edema or intracranial hemorrhage was evident. Her white blood cell (WBC) count was 11,110/ $\mu$ L, her neutrophil segment count was 85.1%, and her C-reactive protein level was mildly elevated at 1.55 mg/dL. No other abnormal findings were notable, except for aspartate transaminase, which rose to 59 IU/L, and hyponatremia with a sodium level of 131.3 mmol/L. Lumbar puncture was performed, and the opening pressure was 40 cmH<sub>2</sub>O. The WBC count in her cerebrospinal fluid (CSF) was 2,060 cells/mm<sup>3</sup> with 62% polymorphonuclear leukocytes, along with a raised protein level of 145 mg/dL and decreased glucose level of <10 mg/dL. Under the suspicion of bacterial meningitis, empirical therapy with vancomycin and cefotaxime was started. Dexamethasone and mannitol were also administered to prevent neurologic complications and to control intracranial hypertension, respectively. The patient's neurologic and gastrointestinal symptoms improved on the second day of her hospital stay, and she remained afebrile from the fifth day to the end of her hospitalization. Brain magnetic resonance imaging and angiography performed on the third day of her hospital admission were normal. No organisms were isolated in blood cultures, but Group D *Salmonella* species were isolated in CSF culture. The species were susceptible to ampicillin, cefotaxime, ceftazidime, trimethoprim/sulfamethoxazole and ciprofloxacin. Considering the pathogen, her stool was examined, yet no organisms including *Salmonella* species were isolated in cultures. Multiplex polymerase chain reaction that detects *Vibrio* species, *Salmonella* species, *Shigella* species, *Campylobacter* species, *E. coli* O157:H7 and verocytotoxin-producing *E. coli* was performed in stool and the result was also negative. To treat acute meningitis due to Group D *Salmonella*, her antibiotic regimen was modified to ceftriaxone monotherapy. Her CSF was sterile on the fourth day of hospital admission, and the

CSF profiles improved to WBC 580 cells/mm<sup>3</sup> with 24% polymorphonuclear leukocytes, along with a protein level of 72.1 mg/dL and a glucose level of 35 mg/dL.

Since *Salmonella* meningitis is very rare in healthy children, the patient's immune status was evaluate; no abnormal findings were noted (immunoglobulin A: 145.82 mg/dL; immunoglobulin G: 987.42 mg/dL; immunoglobulin M: 114.99 mg/dL; CD19: 883.84/μL [31.7%]; CD3: 1260/μL [74.0%]; CD4: 743/μL [44.0%]; CD8: 491/μL [29.0%]; CD16+56: 59/μL [2%]; C3: 129 mg/dL; C4: 16 mg/dL; CH50 48 U/mL; and dihydrorhodamine fluorescence: 100%). Hybridization capture-based next-generation sequencing was performed with the patient's blood specimen to evaluate 51 genes associated with 130 primary immunodeficiency diseases, including IL12B, IL12RB1, IFNGR1, IFNGR2, and STAT3. No significant genetic mutations were observed, except for a c.346C>T (p. Arg116\*) heterozygote mutation, indicating that the patient was a carrier of complement C9 deficiency. There was no remarkable family history suspicious for primary immunodeficiency disease.

Antibiotics were administered for four weeks from the first sterile CSF culture, and the patient was discharged home without any complications. The patient remained healthy without any neurologic sequelae at the five-month follow-up.

This study was approved by the Institutional Review Board of Seoul Metropolitan Government-Seoul National University Boramae Medical Center, and written informed consent was waived (IRB No: 10-2021-124).

## DISCUSSION

The patient in the present case was an 8-year-old girl who was admitted to the emergency room with a chief complaint of high fever and vomiting. Additional accompanying symptoms included headache, abdominal pain, poor oral intake, decreased urination, and abnormal mental status. Signs of meningeal irritation prompted an evaluation for suspicious bacterial meningitis, and Group D *Salmonella* species were isolated in CSF culture. The infection source was presumed to be clams that the patient ate before symptom onset. Considering the rarity of the disease in immunocompetent children, her immune status was assessed, yet no abnormal findings were observed. The patient improved rapidly with intravenous ceftriaxone, and no complications or neurologic sequelae were observed during the five-month follow-up.

NTS infection in immunocompetent hosts usually causes self-limiting enteritis, which commonly accompanies fever, vomiting and nonbloody diarrhea.<sup>1)</sup> However, NTS infection is also associated with diverse illnesses other than enteritis, with a wide range of severities in specific risk groups, including bacteremia and extraintestinal manifestations, such as meningitis, osteomyelitis, septic arthritis, deep soft tissue infection and pneumonia. Bacteremia is the most common systemic infection, and the incidence varies from 2% to 47% of *Salmonella* enteritis according to region.<sup>2)</sup> Meningitis due to NTS occurs far less often, and the exact incidence is unknown. According to the largest multicenter study on pediatric invasive bacterial infections in South Korea, *Salmonella* remains the second most common cause of bacteremia in children 3–59 months of age, despite the overall decrease in the incidence of salmonellosis over the last five years with improved hygiene.<sup>5)</sup> There were no cases of *Salmonella* meningitis; however, to the best of our knowledge, there have been no previous reports on *Salmonella* meningitis in immunocompetent children in Korea.

Few studies on meningitis due to NTS or *S. enterica* ser. Typhi have been published in children, and most of them were in infants and in malnourished children (Table 1). The neurologic symptoms of the patients were diverse, including altered mental state, seizure, or neonatal

**Table 1.** Summary of pediatric cases of *Salmonella* meningitis found in the English medical literature

Articles	Age/Sex	Clinical symptoms	Source of positive culture	Species	Brain imaging	Antibiotics	Outcome
Wu et al. (2011) <sup>4</sup>	Infants <1 yr 24 cases	Fever (100%), Lethargy (25%), irritability (42%), poor feeding (83%), diarrhea (33%), vomiting (3%), bulging anterior fontanel (54%), nuchal rigidity (38%), seizure (63%)	CSF (100%), blood (59%), stool (17%), urine (6%)	<i>Salmonella enteritidis</i> Group D1 (41.7%), <i>Salmonella enteritidis</i> Group B (12.5%), <i>Salmonella enteritidis</i> Group C1 (8.3%), <i>Salmonella enteritidis</i> C2 (4.2%)	Hydrocephalus (50%), subdural collection (42%), cerebral infarction (33%), ventriculitis (25%), empyema (13%), intracranial abscess (8%), cranial nerve palsy (8%)	Third generation cephalosporins (29%), aminoglycoside + third generation cephalosporins (8%), AMP + CHL + third generation cephalosporins (8%), CHL + third generation cephalosporins (17%), AMP + third generation cephalosporins (25%), AMP + CHL (8%), CHL (4%)	Death (13%), ongoing seizure (29%), focal motor weakness (42%), cranial nerve palsy (8%)
Owusu-Ofori et al. (2003) <sup>6</sup>	8 mon/M 9 mon/F	Fever, vomiting Unconscious state, diarrhea, vomiting, generalized tonic clonic seizure	CSF CSF	<i>Salmonella</i> species <i>Salmonella</i> species	Not performed Not performed	PEN, CHL PEN	Death Death
Khurshid et al. (2019) <sup>7</sup>	16 yr/M	Fever, headache, neck rigidity, projectile vomiting, altered mentality	CSF	<i>S. typhi</i>	CT: mild cerebral edema	MEM, MTZ	Slow progression requiring neurological therapy
Bukhari et al. (2021) <sup>10</sup>	9 yr/M	Fever, vomiting, headache, drowsy mental status	CSF	<i>S. typhi</i>	Not performed	MEM, AZM	No sequelae
Singhal et al. (2012) <sup>11</sup>	28 days/M	Fever, lethargy, clonic convulsion	Blood, CSF	<i>S. typhi</i>	MRI: subdural empyema, ventriculitis, ischemic changes in the bilateral periventricular areas	CRO, AMK → MEM, NET	No sequelae
Alkindi et al. (2021) <sup>12</sup>	2 mon/M	Fever, lethargy, poor oral intake, diarrhea	Blood, CSF, stool	Nontyphoidal <i>Salmonella</i>	MRI: mild diffuse smooth pial enhancement	CTX, AMP	No sequelae
Ficara et al. (2019) <sup>13</sup>	2 mon/M	Fever, non-bloody diarrhea, poor oral intake	Blood	<i>Salmonella enteritidis</i>	MRI: periencephalic purulent effusion	CTX	Effusion resolved without sequelae
Truong et al. (2018) <sup>14</sup>	3 mon/F	Fever, irritability, poor oral intake, seizure	Blood, CSF	Nontyphoidal <i>Salmonella</i>	MRI: right occipital horn purulent material without abscess formation, dural enhancement	CRO	No sequelae
Ploton et al. (2017) <sup>15</sup>	3 mon/M	Fever, vomiting, seizure, unilateral hemiparesis	Blood	<i>S. typhimurium</i>	MRI: subdural and frontal cerebral empyema and brain abscess	CTX, CIP	No sequelae
De Malet et al. (2016) <sup>16</sup>	5 yr/F	Fever, vomiting, drowsiness	Blood, CSF	<i>S. newport</i>	Not performed	CRO	No sequelae
Ahmed et al. (2016) <sup>17</sup>	4 mon/F	Fever, loss of consciousness, tonic clonic movement	Blood, CSF	<i>Salmonella</i> species	CT: multiple microabscesses with progressive hydrocephalus	CTX, GEN, AMP → MEM	Mild spasticity with ventriculoperitoneal shunt
Bowe et al. (2014) <sup>18</sup>	3 days/M	Apnea, bradycardia, lethargy	Blood, CSF, stool	<i>S. berta</i>	MRI: hemorrhagic infarction with large territories, uncus and subfalcine herniation	CTX	Death
Fomda et al. (2012) <sup>19</sup>	1 mon/F	Fever, poor oral intake, focal seizure	Blood, CSF	<i>Salmonella enteritidis</i>	CT: normal	CIP, CRO	Recurrence without sequelae
Ghais et al. (2009) <sup>20</sup>	9 mon/F	Fever, focal seizure, watery diarrhea	Stool	<i>S. pomona</i>	MRI: subdural empyema	CRO	No sequelae

Abbreviations: CSF, cerebrospinal fluid; AMP, ampicillin; CHL, chloramphenicol; PEN, penicillin; CT, computed tomography; MEM, meropenem; MTZ, metronidazole; AZM, azithromycin; MRI, magnetic resonance imaging; CRO, ceftriaxone; AMK, amikacin; NET, netilmicin; CTX, cefotaxime; CIP, ciprofloxacin; GEN, gentamicin.

apnea. Although no abnormal findings were observed in brain imaging in our patient, studies have shown that the morbidity of NTS meningitis is high, with subdural empyema, cerebral edema, ventriculitis, cerebral abscess, and hemorrhagic infarction as causes (**Table 1**). Long-term neurologic sequelae may also develop, including developmental delay and motor disabilities, especially in infants who present late and those with prolonged fever.<sup>6)</sup> The mortality rate of *Salmonella* meningitis is also high, ranging from 13% to 60%, depending on age and region.<sup>4,7,8)</sup>

As morbidity and mortality are high in NTS meningitis, it is critical to promptly administer appropriate antibiotics. Third-generation cephalosporins are recommended as first-line antibiotics in children with invasive NTS infections.<sup>1)</sup> To treat NTS meningitis, antibiotics should cross the blood-brain barrier, penetrate into the intracellular space, and have intracellular activity; third-generation cephalosporins have an excellent ability for this.<sup>2)</sup> Fortunately, third-generation cephalosporins are often administered as initial empirical antibiotic therapy in children with presumed bacterial meningitis. Our patient was successfully treated with ceftriaxone for four weeks, and the patient recovered without any complications. For multidrug-resistant NTS meningitis, meropenem and fluoroquinolones can be alternative options.<sup>3)</sup> Three pediatric patients published in the literature with meningitis due to multidrug NTS were all treated with meropenem, and there was clinical improvement. Despite treatment with appropriate antibiotics, the prognosis of NTS meningitis can vary from full recovery to death, and neurological complications, such as cerebral palsy, epilepsy, and focal weakness, are common (**Table 1**).

Invasive *Salmonella* infections occur more frequently in patients with immunocompromising conditions, such as malignant neoplasms, HIV, asplenia, sickle cell disease and chronic granulomatous disease.<sup>2)</sup> Susceptibility to invasive *Salmonella* infection is related to immunological mechanisms involving several cytokines and lymphocytes. As bacteria invade through the intestine, they are recognized by macrophages, which stimulate T cells and NK cells via IL-12 and IL-23 secretion.<sup>9)</sup> Activated T cells and NK cells secrete interferon- $\gamma$  to further stimulate macrophages and eliminate the pathogen through STAT1. Intracellular killing becomes difficult when cytokines are not adequately expressed or lymphocytes are depleted at any stage. This explains the more serious invasive infections in HIV patients and recurrent infections in patients with interleukin (IL)-12 or IL-23 deficiency.<sup>9)</sup> To evaluate possible impairment of the immune system, the patient's immune status was assessed. Basic immunologic test results were normal, and no significant genetic mutation was detected in next-generation sequencing. If the patient later presents with recurrent invasive *Salmonella* infection, more in-depth analysis may be warranted.

In conclusion, we present a rare case of NTS meningitis in an immunocompetent child who recovered well without any complications or neurologic sequelae. *Salmonella* species should be considered in children presenting with suspicious meningitis, especially those exposed to contaminated food and water.

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## 요약

살모넬라 수막염은 소아청소년에서 흔하지 않은 병이나 심각한 신경학적 합병증을 일으킬 수 있다. 영아, 특히 3개월 미만의 연령과 악성 종양, 말라리아 감염, 인체면역결핍바이러스 감염과 같은 면역 저하 상태는 살모넬라 수막염의 위험 인자로 알려져 있다. 본 증례에서는 고열과 구토, 의식 변화를 주소로 내원한 이전 특이병력 없던 건강한 8세 여아의 살모넬라 수막염 증례를 소개한다. 환자의 뇌척수액에서 D군 살모넬라가 배양되었으며, 뇌 자기공명영상 소견은 정상이었다. 면역 글로불린 수치와 림프구 수는 정상 범위였고, 차세대 염기서열 분석에서 원발성 면역결핍 질환을 일으키는 유전자 변이는 검출되지 않았다. 3세대 세팔로스포린 투약으로 환자의 증상은 빠르게 호전되었으며 합병증이나 후유증은 발생하지 않았다. 비장티푸스 살모넬라균은 면역이 정상인 소아에서 수막염을 일으킬 수 있으며 조기에 항생제를 투여하면 성공적으로 치료할 수 있다.