

C A S E R E P O R T

Unusual meningitis caused by non-typhoid *Salmonella* in an Italian infant: a case report

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Summary. *Background:* Non-typhoid *Salmonella* (NTS) is an important cause of bacterial meningitis in newborn and infants in developing countries, but rarely in industrialized ones. We describe an unusual presentation of bacterial meningitis in an infant, focusing on his diagnostic and therapeutic management. *Case report:* An Italian two-month old male presented high fever and diarrhea with blood, associated with irritability. Inflammatory markers were high, cerebrospinal fluid analysis was compatible with bacterial meningitides but microbiological investigations were negative. *Salmonella enteritidis* was isolated from blood. Cerebral ultrasound and MRI showed periencephalic collection of purulent material. Specific antibiotic therapy with cefotaxime was initiated with improvement of clinical conditions and blood tests. Brain MRI follow up improved progressively. *Conclusions:* Most of pediatric patients with NTS infection develop self-limited gastroenteritis, but in 3-8% of the cases complications such as bacteremia and meningitis may occur, especially in weak patients. Cerebral imaging can be useful to identify neurological findings. Although there is no standardized treatment for this condition, specific antibiotic therapy for at least four weeks is recommended. Neuroimaging follow up is required due to high risk of relapse. (www.actabiomedica.it)

Key words: meningitis, non-typhoid *Salmonella*, *Salmonella enteritidis*, developing countries, developed countries, antibiotic therapy, neuroimaging

Most of pediatric patients with Non-typhoid *Salmonella* (NTS) infection develop self-limited gastroenteritis. However, 3-8% of the patients present secondary bacteremia, followed by meningitis, osteomyelitis, endocarditis, arthritis, urinary-tract infection and pneumonia (1, 2). The risk of invasive salmonellosis is higher in case of immunocompromised individuals, patients with hemoglobinopathies and hemolytic anemias or in neonates (3). *Salmonella* is identified as pathogen in 1% or less of confirmed cases of bacterial meningitis in newborn and infants (4). *Salmonella* species are a leading cause of Gram-negative bacterial meningitis in the developing countries, although rarely

seen in developed ones (5), being associated with high complications and mortality rate (4). We describe a NTS meningitis in a two-month old boy focusing on the clinical management and follow up of these rare and severe cases.

Case presentation

An Italian two-month old male infant was admitted to our Pediatric Emergency Department with high fever (TC 39.3°C) irritability, poor appetite and diarrhea with blood traces. His past medical history was

silent. He was bottle fed. The mother had a history of one-day diarrhea without fever two days before.

He presented with pulsating bregmatic fontanel, no neck stiffness; Kernig's and Brudzinski's signs were negative. Chest, cardiac and abdominal examination did not reveal any abnormality. He was admitted to the medical ward with alert for isolation and rapid investigation. Blood test showed mild increase of inflammatory markers (Platelets 498.000/ μ l, RCP 2,8 mg/dl). Lumbar puncture was performed. CSF was turbid with predominating polymorphs (950 cells/ μ l) in association with raised protein (158 mg/dl). Empirical therapy with ampicillin, gentamicin, cefotaxime and acyclovir was started. CSF microbiological investigations (culture and molecular biology) were negative, while *Salmonella enteritidis* was isolated in blood. Antibiotic treatment was shifted to intravenous cefotaxime at 300 mg/kg/die and performed for six weeks. During the first three days of recovery, the patient presented short episodes of staring, followed by irritable crying. Cerebral ultrasound was performed, and revealed periencefalic purulent suffusion, confirmed by the brain MRI (Fig. 1a). Urgent brain MRI excluded the development of intracranial hypertension. Fever decreased after four days of recovery. Many stool samples were collected, but *Salmonella* was never found during the hospitalization. A month later, cerebral MRI showed a persistent frontal purulent suffusion (5 mm diameter) although CFS was negative. At the end of the antibiotic therapy, a third cerebral MRI revealed a partial re-absorption of the frontal collection (Fig. 1b). After the discharge (7 weeks from admission), stool samples revealed the presence of *Salmonella enteritidis*. Blood tests were negative for ongoing or recurring *Salmonella* infections. Cerebral MRI showed a progressive reduction of the frontal purulent material.

Discussion

Most part of the cases of meningitidis caused by *Salmonella* in children reported in literature occur in developing countries. NTS invasive infections have often worse-than-expected outcome, despite adequate antimicrobial therapy, because of multiple factors [Table 1. (6-23)]. Developing countries are endemic areas

for HIV infection, parasitosis (such as schistosomiasis) and sickle cell anemia, known risk factors able to increase the infectious complications (9). Moreover, the delayed beginning of targeted antibiotic therapies and the inadequate duration associated with poor health awareness status, may play a significant role on prognosis (17, 23). High rate of multi-drug resistant *Salmonella* strains makes therapeutic choice difficult (22).

The role of imaging findings in *Salmonella* meningoencephalitis is not clear (24). MRI can be either normal or showing diffuse cerebral vasogenic

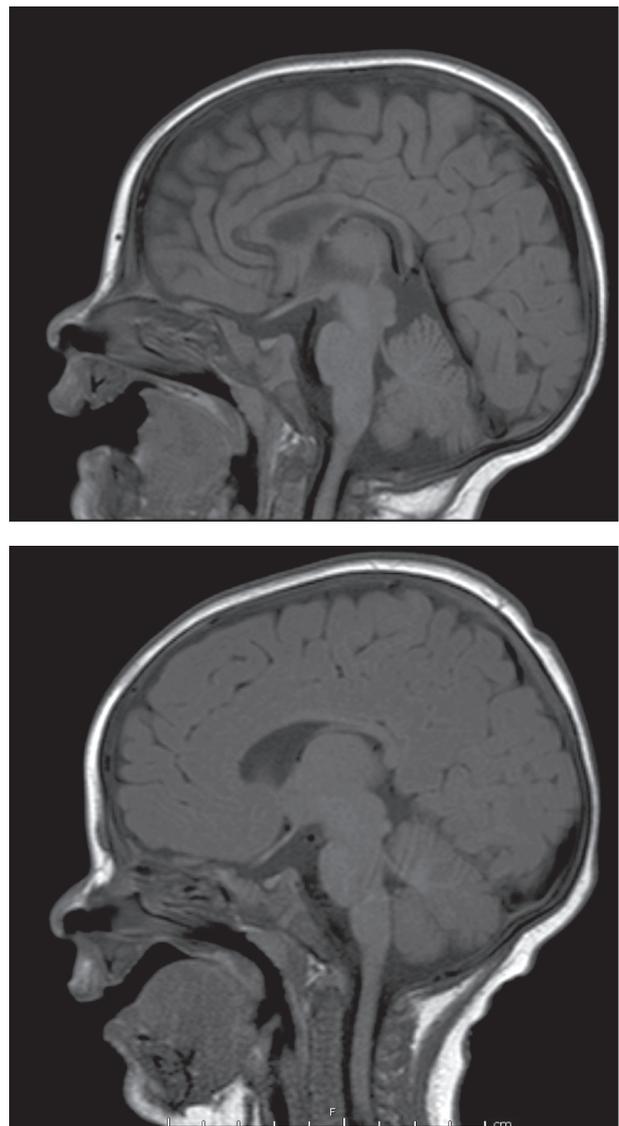


Figure 1. Brain MRI imaging at admission (1a) at the end of the antibiotic treatment (1b).

Table 1. Reports on cases of meningitis caused by Salmonella in the last ten years

Authors	Journal	Year	Antibiotics	Duration	Outcome
Ploton MC et al. (6)	J Paediatr Child Health	2017	Intravenous combination of cefotaxime and ciprofloxacin (for 6 weeks) + ciprofloxacin per os (for 6 weeks)	12 weeks	Good
De Malet et al. (7)	Case Rep Infect Dis	2016	Intravenous cefotaxime (200 mg/Kg/die)	3 weeks	Good
Ricard C et al. (8)	Arch Pediatr	2015	Intravenous ciprofloxacin	15 days	Good
Chacha F et al. (9)	BMC Res Notes	2015	Intravenous ceftriaxone (1 g/die))	2 weeks	Good
Heaton PA et al. (10)	Br J Hosp Med (Lond)	2015	Cefotaxime	6 weeks	Good
Tuan ĐQ et al. (11)	Jpn J Infect Dis.	2015	Case1: ceftriaxone (100 mg/Kg/die) Case2: ceftriaxone (100 mg/Kg/die) + chloramphenicol (100 mg/Kg/die) Case3: imipenem (50 mg/Kg/die) + ciprofloxacin (30 mg/Kg/die) Case4: imipenem + ciprofloxacin, then combination of chloramphenicol and ciprofloxacin	Case 1: 4 weeks Case 2: 7 weeks Case 3: 8 weeks Case 4: 6 weeks	Case 1: recurrence of Salmonella meningitis Case 2: good Case 3: intracranial complications Case 4: good
Bowe AC et al. (12)	J Perinatol.	2014	Cefotaxime	-	Poor (on day 3: poor feeding, lethargy, apnea, bradycardia)
Rai B et al. (13)	BMJ Case Rep	2014	Ceftriaxone	21 days	Good
Adhikary R et al. (14)	Indian J Crit Care Med	2013	Intravenous combination of ceftriaxone, chloramphenicol and ciprofloxacin	After 25 days the patient's therapy was modified because of nosocomial pneumonia	Poor
AJ Johan et al. (15)	Southeast Asian J Trop Med Public Health	2013	Intravenous ceftriaxone, then meropenem because of intracranial complications	Ceftriaxone for 3 weeks Meropenem for 11 weeks	Good
Singhal V et al. (16)	J Clin Diagn Res	2012	Intravenous combination of ceftriaxone and amikacin, then meropenem and netilmycin because of neurological complications	Ceftriaxone plus amikacin for 3 weeks Meropenem plus netilmycin for 14 days	Good
Fomda BA et al. (17)	Indian J Med Microbiol	2012	Intravenous combination of ciprofloxacin (10 mg/Kg twice daily) and ceftriaxone (100 mg/Kg/die)	3 weeks, then other 6 weeks because of recurrent meningitis	Good

(continued)

Table 1 (continued). Reports on cases of meningitis caused by Salmonella in the last ten years

Authors	Journal	Year	Antibiotics	Duration	Outcome
Olariu A et al. (18)	BMJ Case Rep.	2012	Intravenous ceftriaxone (80 mg/Kg/die once a day)	3 weeks	Good
Wu HM et al. (19)	BMC Infect Dis	2011	Most of patients of this study received third-generation cephalosporins, combined with chloramphenicol or ampicillin	-	-
Ghais A et al. (20)	Eur J Pediatr	2009	Intravenous ceftriaxone	4 weeks	Good
Guillaumat C et al. (21)	Arch Pediatr.	2008	Intravenous combination of third-generation cephalosporins and quinolones	At least 3 weeks	-
L. Sangaré et al. (22)	Bull Soc Pathol Exot.	2007	56 cases of meningitis by Salmonella: third-generation cephalosporins and aminoglycosides effective	-	Neurological complications only in one case treated with ceftriaxone and chloramphenicol
Bayraktar MR et al. (23)	Indian J Pediatr.	2007	Meropenem	-	Poor (death on the second day after the initiation of meropenem therapy: diagnostic delay?)

edema, edema of splenium, and focal white matter edema associated with cerebritis (25). MRI can be useful to identify neurological complications associated with Salmonella meningitis such as subdural effusion/empyema, abscesses, ventriculitis, cerebritis, hydrocephalus, venous thrombosis, and infarct (26). In our case, MRI showed a periencefalic collection of purulent material, then resolved. Neurological complications and sequelae (mental retardation, different forms of cerebral palsy, visual and hearing deficit) are very common (27). A retrospective study analyzed the long-term outcomes of the cases of Salmonella meningitis from 1982 to 1994 in Taiwan. Among the twenty-four patients, fifteen presented seizures before their admission to the hospital, and thirteen during the hospitalization. Acute complications included prolonged seizures (100%), hydrocephalus (50%), subdural collection (42%), cerebral infarction (33%),

ventriculitis (25%), empyema (13%), intracranial abscess (8%), and cranial nerve palsy (8%). Three patients died. The long-term neurological sequelae consisted of language disorders, motor disability, mental delay, epilepsy, sensorineural hearing loss, visual deficits, abducens nerve palsy, microcephaly, and hydrocephalus (19). In our case, the patient is following periodic clinical controls, but up to now his neurological development results normal. Neuroimaging studies are recommended for every case of Salmonella meningitis even if the patient has presented an apparent clinical resolution and optimal response to antibiotics, due to risk of relapse (5).

There are different recommendations about the need of further CSF examination. Price et al. suggest routine follow-up lumbar punctures after the first negative CSF culture only if clinically indicated (4). According to the normalization of brain MRI after two

months from the treatment ending, we decided not to perform a new lumbar puncture.

Medical treatment of meningitides caused by Salmonella is very difficult and not standardized. In 2003, Owosu-Ofori et al. described two cases of Salmonella meningitis, suggesting that conventional antibiotics (ampicillin, chloramphenicol and cotrimoxazole) had a minimal role in treatment Salmonella meningitis (they had a cure rate of 41.2%, a relapse rate of 11.8%, and an associated mortality of 44.7%). One of the problems with chloramphenicol is that it is bacteriostatic against Salmonella. Optimum management of bacterial meningitis requires antibiotic(s) with bactericidal action (28). Fluoroquinolones (ciprofloxacin) showed a cure rate of 88.9%, while the third-generation cephalosporins (cefotaxime or ceftriaxone) had a cure rate of 84.6%. One of the main concerns in using ciprofloxacin is its potential joint toxicity and cartilage destruction in children. Fluoroquinolones have a lot of positive aspects: high bioavailability (near 100%) following oral administration, excellent penetration into many tissues (including CSF and brain), and good intracellular diffusion. The American Academy of Pediatrics recommends the treatment for Salmonella meningitis with cefotaxime or ceftriaxone with or without fluoroquinolone for 4 weeks or more. However, cases of relapse following the four-week treatment have been reported. A combination of ciprofloxacin and ceftriaxone or cefotaxime has been suggested especially for the treatment of cerebral abscesses by Salmonella spp (4).

Conclusion

We described a rare case of NTS infection in an immunocompetent patient living in an industrialized country. The infant developed meningitis as complication of systemic infection probably due to his early age. According to our experience, an early diagnosis based on recognition of acute neurological signs and laboratory findings associated to a prompt and appropriated antibiotic therapy for at least four to six weeks can improve the outcome of the patient and reduce the risk of neurological sequelae. Neuroimaging follow up together with accurate neurological clinical examina-

tion, is required to prevent and reduce the high risk of relapse.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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