Subdural collections due to non-typhi *Salmonella* infections in two Malaysian children

Intan HI, Zubaidah CD, Norazah A, Norlijah O

ABSTRACT

Subdural collections caused by *Salmonella* infection are rarely encountered in children. We present two cases caused by non-typhi *Salmonella*, one a four-and-a-half-month-old boy presenting with subdural effusion, and the other, a 16-month-old boy with empyema. The diagnosis was confirmed on blood and subdural pus cultures. One patient had status epilepticus following focal fit, and the other had prolonged fever without any localising signs of infection on admission. They responded well to prompt surgical drainage and prolonged systemic antibiotic therapy. Contrary to previous reports, both patients showed favourable outcome in terms of neurological sequelae.

Keywords: cerebral infection, non-typhi *Salmonella*, subdural effusion, subdural empyema

Singapore Med J 2008; 49(7): e186-e189

INTRODUCTION

Focal central nervous system infections caused by *Salmonella* are uncommon manifestations in children. The intracranial infections can be in the form of meningitis, subdural effusions, subdural empyema (SDE), epidural empyema and brain abscess. We present the first reported series of cases of subdural collections caused by non-typhi *Salmonella* infection in Malaysian children presenting as bilateral subdural effusions and left SDE, respectively.

CASE REPORTS

Case 1

A four-and-a-half-month-old boy presented at a local hospital with a prolonged episode of left-sided seizure preceded by a three-day history of fever, cough and vomiting. He had no history of head trauma or any known source of infection. He was taken care of by a baby-sitter while both parents were at work. His immunisation was up-to-date and his development was appropriate. His maternal cousin had epilepsy with delayed development. His status epilepticus was controlled with phenytoin and phenobarbitone therapy. Ceftriaxone was commenced to cover for possible meningitis. He further required mechanical ventilation for cerebral protection. An urgent cranium computed tomography (CT) showed bifrontal subdural effusions, which prompted the transfer to the neurological team for surgical drainage.

Physical examination revealed a sedated and febrile child. His anterior fontanelle was bulging and tense, with a head circumference of 43 cm, corresponding to the 50th percentile of the head circumference-for-age percentiles chart. He was hypertonic and hyper-reflexic, his pupils were reactive and fundoscopic examination was normal. There was hepatosplenomegaly with lymphadenopathy. The remainder of the examination was normal. The full blood count (FBC) revealed anaemia (haemoglobin 9.8 g/dL), neutrophilic leucocytosis (total white blood cell 21.8 × 10^9/L; 65.8%) and thrombocytosis (platelets 480,000). The prothrombin time was slightly prolonged (13.7 sec; normal 10.1–12.9 sec), with normal activated partial thromboplastin time. Renal and liver function tests were normal.

Right burrhole and subdural evacuation were performed, which drained high-pressure xanthochromic fluid. Microscopical examination yielded heavily blood-stained fluid, not suitable for cell count. Biochemistry examination showed low glucose (0.6 mmol/L), high protein (7.44 g/L) and positive globulin. Ceftriaxone (50 mg/kg/dose) twice daily was started empirically. He was extubated two days later, however, the fever persisted. Postoperative brain CT showed re-accumulation of subdural collection, which led to the insertion of a left subdural peritoneal shunt. The subdural fluid was still xanthochromic with cell counts of 90 polymorphs.

The first blood culture at the local hospital grew *Salmonella enteritidis*, which was sensitive to ampicillin, chloramphenicol, cotrimoxazole, ceftrioxone and ciprofloxacin. However, urine, stool and subdural fluid cultures were persistently negative. Ceftriaxone was continued for a total of four weeks. He was discharged with an eight-week course of oral therapy, initially constituted of chloramphenicol, but subsequently replaced with ampicillin as the child

Department of Paediatrics, Faculty of Medicine and Health Sciences, University Putra Malaysia, Serdang 43400, Malaysia

Intan HI, MD, MPaeds
Specialist and Lecturer

Norlijah O, MBBS, MRCP
Consultant in Infectious Diseases and Head

Department of Diagnostic Imaging, Institute of Paediatrics, Hospital Kuala Lumpur, Kuala Lumpur 50586, Malaysia

Zubaidah CD, MRadiol
Specialist

Bacteriology Unit, Infectious Diseases Research Centre, Institute for Medical Research, Jalan Pahang, Kuala Lumpur 50588, Malaysia

Norazah A, MSc, PhD
Medical Microbiologist
Consultant and Head

Correspondence to:
Dr Intan Hakimah Ismail
Tel: (60) 3 8947 2610
Fax: (60) 3 8948 9369
Email: ihakimah@yahoo.com

could not tolerate the former antibiotic. Follow-up at 12 weeks revealed a healthy child with good weight gain. His development was corresponding to a nine-month old infant. Repeat brain CT showed no residual subdural effusions.

Case 2

A previously-well 16-month-old Punjabi boy presented to our hospital with a three-day history of fever and rhinorrhoea, for which he was initially treated for pharyngitis. He later became irritable, less active with reduced feeding and slept most of time. Ceftriaxone was started empirically on admission to cover for possible meningitis. Cerebrospinal fluid (CSF) examination, biochemistry, latex agglutination and culture were normal. In spite of the antibiotic therapy, he continued to have swinging pyrexia without marked clinical improvement. He was investigated for possible causes of prolonged fever—tuberculosis, typhoid fever, hidden abscesses, malignancy and connective tissue diseases. After 11 days in the ward, due to personal and social reasons, his mother insisted on an at-own-risk discharge.

He was readmitted three days later with unresolved fever and instability; he tended to fall from a sitting position, and refused to walk. He was more irritable and held his head up, as though in pain. There were no seizures, abnormal movements or signs of increased intracranial pressure (ICP). On physical examination, he was pale, irritable and febrile, with instability on sitting posture. He had bilateral cervical and axillary lymphadenopathies with no hepatosplenomegaly. His pupils were equal and fundoscopy was normal. He had no weakness or paucity of movement. His reflexes were brisk, but the tone was normal and Babinski reflex was equivocal. The remainder of the examination was normal.

FBC yielded worsening anaemia (haemoglobin 10.2 g/dL which decreased to 7.7 g/dL), leucocytosis (white blood cell count 32.6×10^9/L to 22.9×10^9/L) with neutrophils predominant (64.4% which decreased to 59%) and thrombocytosis (platelets 509×10^9/L which increased to $1,400 \times 10^9$/L). The full blood picture was reported as normochromic normocytic anaemia secondary to chronic disease with leucocytosis and thrombocytosis, as a response to infection. C-reactive protein was high (26 mg/dL); however, repeated blood, stool and urine cultures were sterile. Liver and renal functions were normal. Chest radiograph was normal, while abdominal ultrasonography showed no evidence of intra-abdominal abscess, and echocardiography reported as no evidence of vegetation. Urgent cranial CT showed a large collection in left frontoparietal-temporal convexity with thick enhancing wall consistent with SDE, and mass effect with midline shift to the right.

Left frontal burrhole was performed and purulent subdural material was drained. The cell count was 20 cells/mm^3 with very high protein (43.0 g/L), and low glucose (0.8 mmol/L) content. *Salmonella paratyphi B* was isolated from the pus. It was sensitive to ceftriaxone, chloramphenicol, ampicillin, cotrimoxazole and ciprofloxacin. His tuberculosis work-up, connective tissue screening, immune parameters, serology tests for Epstein-Barr virus and parvovirus as well as blood and CSF for fungal infection were negative. Treatment with ceftriaxone (50 mg/kg/dose) twice daily was continued for a total of three weeks. His fever subsided the following day of drainage. A repeat cranial CT showed residual empyema. He was discharged well, with no neurological deficit. Oral ciprofloxacin was planned for a further six to eight weeks. CT brain was to be repeated at six weeks of antibiotics, unfortunately, he did not turn up and defaulted follow-up.

DISCUSSION

Focal intracranial infections are unusual manifestations of salmonellosis. Up to the year 2002, only around 80 cases have been reported in the literature,[1] and most of them were caused by *Salmonella typhi*, but not infrequently, non-typhi *Salmonella* (NTS) species were also isolated.[1] In developing and tropical countries like Africa, Brazil and Thailand, NTS is an important and common cause of Gram-negative bacteraemia in children less than five years of age,[2] as well as septicaemia and intracranial infections in neonates and young infants,[3] but it is uncommon in economically-developed communities.

NTS intracranial infections are associated with a high mortality, significant neurological sequelae in those who survive, and high treatment failure rates.[3-5] The highest case-fatality rate occurred among immunocompromised infants, whereas the rates were lower for immunocompromised children and non-immunocompromised infants.[6] Cell-mediated immunity (CMI) is important in the protection against *Salmonella* infection. T-lymphocytes recognise the antigen and activate macrophages via cytokine release to enhance bactericidal killing. An effective T helper 1 cell response is necessary for the killing of intracellular *Salmonella* by macrophages.[2] Thus, young age and conditions that suppress CMI and reduce intestinal mucosal integrity, such as human immunodeficiency virus infection and malnutrition, predisposes one to NTS invasive disease.[2]

The intracranial infections can be in the form

Table 1. Clinical epidemiological data of neurological manifestations of non-typhi Salmonella reported in the literature.

Ref. no.	No. cases	Clinical presentations	Blood culture	CSF/subdural fluid culture	CT / US brain findings	Location	Outcome
Current study	2 infants	Focal fit with status epilepticus (Case 1); prolonged fever, irritability, later signs of instability and refused to walk (Case 2); no history of typhoid fever in both cases	*S. enteritidis* (Case 1); negative (Case 2)	*S. paratyphi B* (Case 2); negative (Case 1)	Bifrontal subdural effusions (Case 1); left subdural empyema (Case 2)	Malaysia	Good in both cases
1	6 cases (4 infants and 2 adults)	History of typhoid fever and meningitis (2 infants), recent fever (6), focal convulsions (3 infants, 1 adult), hemiparesis (3 infants, 2 adults), tense fontanelle (all infants), papilloedema (2 adults, 1 infant)	*S. typhi* (in 2 infants with typhoid fever and meningitis); 4 other cases were sterile	*S. typhi* (2 infants, 1 adult); *S.* group D (1 infant, 1 adult); no organisms in 1 infant)	Subdural empyema (4); subdural empyema with delayed venous infarct and hydrocephalus (1 infant); subdural effusions (1 infant)	3 from India and 3 from Oman	Good (5); satisfactory with residual hemiparesis (1 infant)
3	28 infants	Fever (28), convulsion (20), bulging fontanelle (5), nuchal rigidity (4), coma (1)	Not stated	*S. panama* (6), *S. enteritidis* (3), *S. krefeld* (3), *S. derby* (2), *S. blockey* (2), *S. typhimurium* (1), *S. hvittingfoss* (1), *S. poonar* (1), *S. stanley* (1), *S. tennessee* (1), *S. virchow*(1), and other serovar (2)	Subdural empyema or effusion (20), ventriculitis (5), cerebritis (5), brain abscess (2)	Thailand	Severe neurological deficit (6); died (3)
5	13 infants	Fever (13), preceding diarrhoea (6), vomiting (4), irritability (3), fits (9), intractable seizures (6)	6 positive (type of organisms not stated)	*S. enteritidis* (5), *S. oslo* (1), *S.* spp. (1), *S. stanley* (1), *S. paratyphi B* (1), *S. matopeni* (1), *S. oranienberg* (1), *S. virchow* (1), *S. hadar* (1)	Subdural effusions (4); subdural empyema (3); cerebral abscess (1); ventriculitis (1); hydrocephalus (5)	Malaysia	Good (5); developmental delay and cerebral palsy (4); died (2); discharged at own risk (2)
10	1 infant	Fever, reduced feeding, diarrhoea	Negative	*S. enteritidis*	Bifrontal subdural empyema	Japan	Good
11	1 infant	Fever, irritability, circulatory failure, purpura fulminans	*S.* group B	*S.* group B	Subdural empyema, ventriculitis, later brain abscess	Taiwan	Died

S.: *Salmonella*

of meningitis, subdural effusions, SDE, epidural empyema and brain abscess. Brain abscess occurs more often in adults; in contrast, meningitis and subdural collections (effusion and empyema) present more often in children, especially in infants.[1,7] Until the year 2000, only 35 cases of SDE had been reported.[1] For subdural collections, the predisposing factors include meningitis, subdural haematoma, trauma, sinusitis, otitis and mastoiditis,[7] though many cases did not have any precipitating factors. Our patients also did not have any of these factors, and in fact in Case 2, the initial CSF biochemistry was normal and the culture did not grow any organism.

Large numbers of cases of non-typhoidal salmonellosis may not have an obvious history of *Salmonella* infections.[1] Similar to our cases, there were no signs and symptoms to suggest gastroenteritis, such as preceding diarrhoea, bloody stools, vomiting, or abdominal pain. A triad of fever, bacteraemia and meningitis are the most common

clinical manifestations,[5,7] followed by altered consciousness and focal neurological deficits.[7,8] Evidence of increased ICP and seizures are less commonly reported.[5,7,8] At times, clinical diagnosis can be difficult as patients may not have signs of meningism or focal neurological deficits, as reported by Yen et al.[9] Our patients had focal convulsion with status epilepticus requiring ventilation (Case 1), and prolonged fever without an obvious source of infection (Case 2). The clinical epidemiological data of NTS neurological manifestations reported in the literature are further illustrated in Table I. The frequently-isolated NTS species from the blood or subdural pus culture are *Salmonella enteritidis* [5,7,8,10] and *Salmonella typhimurium*.[4,7] Other serotypes include *Salmonella* Group D[1] and *Salmonella* Group B.[11] In our patients, NTS serotype enteritidis was isolated from the blood in Case 1, and serotype paratyphi B was obtained from the pus in Case 2.

The advent of CT and magnetic resonance imaging have made them the radiological studies of choice for the diagnosis of subdural collections, in particular, SDE. Cranial CT with intravenous contrast shows a crescent-shaped subdural collection with an enhancing margin around the fluid. The most commonly-located SDE is above the tentorium, and most of them are interhemispherical or lie over the convexities. SDE is almost always unilateral,[1,8,11] and is rarely bilateral.[10] CT of our patient (Case 2) revealed a large collection in the left frontoparietal-temporal convexity with a thick enhancing wall, consistent with SDE. The treatment modalities of choice for subdural collections constitute long-term appropriate antibiotics[1,5] and surgical evacuation, and sometimes repeated drainage is required. Third generation cephalosporins are the antimicrobial of choice in treating intracranial salmonellosis.[1,3,5] The American Academy of Pediatrics recommends that treatment for *Salmonella* meningitis with cefotaxime or ceftriaxone should continue for four weeks or more.[12] Recrudescence and relapse were common when duration of treatment was inadequate or when ampicillin with either chloramphenicol or cotrimoxazole were used as initial therapy.[3,5] Our patients required pus drainage only once, and received cephalosporins for three to four weeks intravenously, followed by oral antibiotics for another six weeks. Both patients had no neurological deficits upon discharge. Subsequent follow-up for Case 1 showed a child with normal neurodevelopment.

In summary, all patients with pyrexia of unknown origin or prolonged fever should be adequately investigated for *Salmonella* aetiology, as well as other causes. The major issues concerning *Salmonella* intracranial infections were its high mortality,[1,5] high treatment failure rates,[3-5] and significant morbidities in the survivors.[6-7] A prompt diagnosis of *Salmonella* subdural collections together with an adequate surgical evacuation, and the appropriate choice of antibiotic at initial presentation followed by its prolonged therapy, will reduce the mortality and morbidity of the disease.

REFERENCES

1. Mahapatra AK, Pawar SJ, Sharma RR. Intracranial Salmonella infections: meningitis, subdural collections and brain abscess. A series of six surgically managed cases with follow-up results. Pediatr Neurosurg 2002; 36:8-13.
2. Graham SM, Molyneux EM, Walsh AL et al. Nontyphoidal Salmonella infections of children in tropical Africa. Pediatr Infect Dis J 2000; 19:1189-96.
3. Sirinavin S, Chiemchanya S, Vorachit M. Systemic nontyphoidal Salmonella infection in normal infants in Thailand. Pediatr Infect Dis J 2001; 20:581-7.
4. Lee WS, Puthucheary SD, Parasakthi N. Extra-intestinal non-typhoidal Salmonella infections in children. Ann Trop Paediatr 2000; 20:125-9.
5. Lee WS, Puthucheary SD, Omar A. Salmonella meningitis and its complications in infants. J Paediatr Child Health 1999; 35:379-82.
6. Sirinavin S, Jayanetra P, Thakkinstian A. Clinical and prognostic categorization of extraintestinal non-typhoidal Salmonella infections in infants and children. Clin Infect Dis 1999; 29:1151-6.
7. 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 1986; 8:31-41.
8. Dunn DW, Mc Allister J, Craft JC. Brain abscess and empyema caused by Salmonella. Pediatr Infect Dis 1984; 3:54-7.
9. Yen MH, Huang YC, Chou ML. Non-typhoid Salmonella empyema in children: report of two cases. J Microbiol Immunol Infect 1999; 32:289-91.
10. Okudera H, Toba Y, Kyoshima K. Bilateral subdural empyema due to Salmonella enteritidis in an infant. Childs Nerv Syst 1989; 5:45-6.
11. Hou JW, Teng RJ, Lee CY. Salmonella meningitis complicated with subdural empyema, brain abscess and purpura fulminans: report of one case. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1989; 30:408-13.
12. American Academy of Pediatrics. Committee on infectious diseases. Salmonella infections. In: Red Book 2000: Report of the Committee on Infectious Diseases. 25th ed. Elk Grove, IL: American Academy of Pediatrics, 2000: 501-6.