Salmonella enterica serovar Panama meningitis in exclusive breastfeeding infants

Report of 4 cases, clinical features and therapeutic challenges

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Abstract

Rationale: The pathway of Nontyphoid Salmonella meningitis, especially in exclusive breastfeeding infants, has not been well characterized.

Patient concerns: We analyzed data related to nontyphoid Salmonella meningitis in 4 infants.

Diagnoses: No diarrhea was observed and the coproculture was negative for all patients.

Interventions: Early diagnosis and treatment with combination of third-generation cephalosporins plus quinolones for a minimum of 3 weeks is necessary to avoid severe sequelae and death.

Outcomes: The first 3 patients had a good evolution, whereas the last patient had multiple brain abscesses and hydrocephalus requiring treatment with a ventriculoperitoneal shunt.

Lessons: The highlights of our study are that all infants were exclusively breastfed, no diarrhea observed and the negative coproculture for all 4 patients, which is relatively rare for Salmonella infection.

Abbreviations: 3GC = third-generation cephalosporin, CSF = cerebrospinal fluid, DNA = deoxyribonucleic acid, HIV = human immunodeficiency virus, PCR = polymerase chain reaction.

Keywords: case reports, exclusive breastfeeding, infant, meningitis, Salmonella panama

1. Introduction

Nontyphoid Salmonella meningitis remains a threat for infants below 2 years of age in both developing and developed countries. However, the pathway of such infections, especially in exclusive breastfeeding infants, has not been well characterized. Salmonella enterica subsp. enterica serovar Panama was isolated for the first time as part of a food-borne outbreak among soldiers stationed in Panama in 1934.[1] Since then, Salmonella panama was isolated from food, animals, and water. It belongs to serogroup D1 and causes gastroenteritis in humans. This serotype especially has been associated with invasive diseases such as bacteremia and meningitis in children.[2] Infections usually occur after eating contaminated food or consumption of contaminated breast milk. In French Guiana, nearly 50% of Salmonella meningitis, especially in exclusive breastfeeding infants, has not been well characterized, Salmonella enterica was isolated from patients.[3] Moreover, nearly 2/3 of them have also been isolated from patients.[3]

Here, we analyzed data related to nontyphoid Salmonella meningitis in infants in our center in order to clarify the comprehensive features of nontyphoid Salmonella meningitis, including clinical characteristics, acute complications, and long-term outcome.

2. Patients and methods

Cayenne Hospital is as a referral center for primary care facility situated in Cayenne the main city of in French Guiana. From 2011 to 2016, we identified 4 cases of Salmonella meningitis referred to the Paediatrics and Surgery Unit. Medical records of the 4 pediatric cases admitted with spontaneous Salmonella meningitis were reviewed. The entry criteria for diagnosis were the isolation of Salmonella species in cerebrospinal fluid (CSF) culture, which further supported infection based on pleocytosis (>30/μL) with predominant neutrophilia and hypoglycorrachia. Other following informations were retrieved: clinical presentations, demographic features, laboratory data, acute complications at hospitalization, antibiotic therapy, and long-term outcomes.

Moreover, for each case, family Salmonella contact exposure was investigated through bacteriological analysis of water, breast milk, and feces.
2.1. Biological methods

Hemoculture and coproculture were used as complementary examinations for the isolation of Salmonella. Identification of Salmonella spp. was based on conventional techniques as well as automated instruments including Vitek-2 (bioMérieux, Marcyl’Etoile, France), API 20 NE method (bioMerieux) or recently mass spectrometry (Microflex, Bruker Daltonics, Bremen, Germany).

The EvaGreen real-time polymerase chain reaction (PCR) assay has been used for identification of S. enterica subsp. enterica serovar Panama. Total deoxyribonucleic acid (DNA) was extracted from the Salmonella spp. isolated strains with the Wizard Genomic DNA purification kit (Promega, Fitchburg, WI). The DNA was resuspended in a rehydration buffer provided with the Wizard kit. The Singleplex PCR was performed in a reaction volume of 50 μL containing DNA (2 μL for the InstaGene matrix or 1 μL diluted 10-fold for Wizard). This molecular characterization of S. enterica serotype was performed at the Enteric Bacterial Pathogens Unit of the Institut Pasteur, Paris, France.¹³

2.2. Ethical consideration and regulatory

Patients’ medical records were retrospectively reviewed, and all data collected were anonymized in standardized forms according to procedures of the Commission Nationale de l’Informatique et des Libertés (the French information protection commission). Moreover, all the participants have signed informed consent, before participating in the study.

3. Results

We have reviewed 4 medical charts of 4 infants admitted for Salmonella meningitis in our center. They did not receive any treatment before admission to the hospital. All the 4 cases met the diagnosis criteria of Salmonella meningitis (isolation of Salmonella in the CSF, pleiocytisis, and hypoglycorachia). Data about the acute phase of Salmonella meningitis were summarized in Table 1. Human immunodeficiency virus (HIV) infection and other risk factors for invasive disease were absent in our cases. Our 4 patients had an atypical clinical presentation: all had fever with vomiting, between 1 and 7 days before diagnosis. None of them had presented diarrhea. Two of them presented seizures before admission to hospital. All had signs of septic shock at admission. Neurological signs like lethargy, irritability, and bulging anterior fontanel were present in all patients. Biological signs were not different from other bacterial meningitis. No diarrhea was observed and the coproculture was negative for all patients. The laboratory findings were listed in Table 1. The clinical strains of S. panama were isolated from the CSF of all the infants. The investigation of the family Salmonella contact exposure was negative for all the patients.

During hospitalization, all the children had a brain magnetic resonance imaging and computerized tomography scan to detect acute intracranial complications and to diagnose ventriculitis. Table 1 summarizes the acute complications and outcomes in our patients with Salmonella meningitis. The 3 first patients had a less severity of the disease with a good evolution, whereas the last patient had multiple brain abscesses and hydrocephalus requiring treatment with a ventriculoperitoneal shunt. He also had deafness and lack of eye tracking. We have noted no deaths.

4. Discussion

Lumbar puncture is easily performed in children, but sometimes the clinical presentation of meningitis may be atypical and delay its completion. The highlights of our study are that all infants were exclusively breastfed, no diarrhea observed and the negative coproculture for all the 4 patients, which is relatively rare for Salmonella infection.

Several studies⁵,⁶ have reported cases with digestive infection in the previous days and a positive coproculture for salmonella. In all patients, we were able to make an etiological investigation of the source of salmonella (coproculture among parents and siblings, study of consumed water). This etiological research was negative. None of these families amounted turtles or snakes. We

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Table 1

| Variables                                      | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|------------------------------------------------|-----------|-----------|-----------|-----------|
| Admission features                             |           |           |           |           |
| Year of occurrence                             | 2011      | 2012      | 2013      | 2016      |
| Sex                                            | F         | F         | F         | M         |
| Breastfeeding                                  | Yes       | Yes       | Yes       | Yes       |
| Age at onset, mo                               | 3         | 6         | 6         | 7         |
| Immune deficiency                              | No        | No*       | No        | No        |
| Sickle cell disease                            | No        | No        | No        | No        |
| Born from a HIV-infected mother                | No        | No        | No        | Yes       |
| Duration of fever before diagnosis, d          | 7         | 7         | 1         | 5         |
| Temperature on admission, °C                   | 39        | 39        | 39        | 38.5      |
| Diarrhea                                       | No        | No        | No        | No        |
| Vomiting                                       | Yes       | Yes       | Yes       | Yes       |
| Seizures before admission                      | No        | No        | Yes       | Yes       |
| Seizures at hospital                           | No        | No        | Yes       | Yes       |
| Lethargy                                       | Yes       | Yes       | Yes       | Yes       |
| Irritability                                   | Yes       | Yes       | Yes       | Yes       |
| Poor feeding                                   | Yes       | Yes       | Yes       | Yes       |
| Bulging anterior fontanel                      | Yes       | Yes       | No        | No        |
| Septisshoc                                     | No        | Yes       | Yes       | Yes       |

(continued)
Table 1 (continued).

| Variables | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|-----------|-----------|-----------|-----------|-----------|
| Antibiotic before hospitalization | No | No | No | Yes |
| Duration of hospitalization, days | 19 | 21 | 22 | 47 |
| Dosing of Quinolone/3GC, mg/kg/d | 45/300 | 45/300 | 45/300 | 45/300 |
| Duration of treatment, d | 19 | 21 | 21 | 45 |
| Condition at discharge | | | | |
| Survival | Yes | Yes | Yes | Yes |
| Disability | No | No | No | Yes |
| Ongoing seizure | No | No | Yes | Yes |
| Focal motor weakness | No | No | No | Yes |
| Relapse | No | No | No | No |
| Acute complications and outcomes | | | | |
| Level of consciousness | | | | |
| Coma in hospital | No | No | Yes | Yes |
| Intracranial complications | | | | |
| Subdural collection | No | No | No | No |
| Intracranial focal infection | No | No | No | Yes |
| Empyema | No | No | No | No |
| Brain abscesses | No | No | No | Yes |
| Cerebral infarction | No | No | No | Yes |
| Ventriculitis | No | No | No | No |
| Hydrocephalus | No | No | No | Yes |
| Long-term outcome development | | | | |
| Delayed | No | No | No | Yes |
| Motor disability | | | | |
| Severe | No | No | No | Yes |
| Moderate | No | No | No | No |
| Mild | No | No | No | No |
| Normal | Yes | Yes | Yes | No |
| Hearing problems | No | No | No | Yes |
| Epilepsy | No | No | No | Yes |
| Microophalphy | No | No | No | Yes |
| Hydrocephalus | No | No | No | Yes |
| Visual deficit | No | No | No | Yes |
| Speech language | No | No | No | Yes |
| Abnormal | No | No | No | Yes |
| Normal | Yes | Yes | Yes | No |
| Biological data | | | | |
| Peripheral blood data | | | | |
| Total WBC, G/L | 7.7 | 9.0 | 3.3 | 3.6 |
| Neutrophils, G/L | 6.31 | 5.94 | 0.36 | 1.34 |
| Lymphocytes, G/L | 0.89 | 2.70 | 2.44 | 2.05 |
| Platelet, G/L | 306 | 182 | 239 | 101 |
| Hemoglobin level, G/dL | 10.6 | 9.3 | 7.3 | 10.4 |
| Ferritin, μg/L | 6.1 | | | |
| CRP, mg/L | 140 | 212 | 191 | 270 |
| Hemoglobin electrophoresis | AA | AA | AA | AA |
| IgG level, G/L | 6 | 5 | 6 | 7 |
| IgA level, G/L | 0.6 | 0.9 | 0.8 | 0.7 |
| HIV | Negative | Negative | Negative | Negative |
| CSF data | | | | |
| Total WBC, μL | 450 | 498 | 70 | 840 |
| PMN, μL | 252 | 149 | 25 | 647 |
| Glucose, mmol/L | 0.4 | 0.2 | 1.9 | <0.1 |
| Protein, G/L | 1.53 | 1.26 | 1.93 | 2.92 |
| Coproculture | Negative | Negative | Negative | Negative |
| Hemoculture | Negative | Negative | Positive | Positive |
| Gram coloration | GN | GN | GN | GN |
| Gram-negative bacterium identified | S. panama | S. panama | S. panama | S. panama |

3GC = third-generation cephalosporins, CSF = cerebrospinal fluid, GN = gram-negative, PMN = polymorphonuclea, WBC = white blood cells.

*Full immunological investigation including congenital or acquired immunodeficiency.*
could not find *Salmonella* in pet-reptiles. In French Guiana, domestic reptiles (snakes, turtles, etc.) are common in houses and their presence near habitations is a usual situation.[3] Exposure to domestic reptiles was involved in the contamination of infants by *Salmonella*.[3,7] Our investigations have not allowed us to find source of salmonella in these infants who were exclusively breastfed. However, a reptilian source of contamination has previously been investigated in French Guiana, and the overall frequency of carriage was 23.2%.[3]

Furthermore, some questions remain unanswered and in particular, scarcity of such infections in infants could be related to a low inoculum? None of the patients had an immune deficiency. The diagnosis of meningitis is easy with lumbar puncture performed in infants with septic shock. The serotype identification of *Salmonella* was made in the National Reference Center for *Salmonella* in France. *S. enterica* subsp. *enterica* serovar Panama was isolated for all of the patients. This serotype is known to cause invasive diseases such as meningitis in children.[1,2]

The currently recommended first-line treatment of *Salmonella* meningitis is a combination of third-generation cephalosporins (3GC) with quinolones for a minimum of 3 weeks.[8] This protocol was conducted for the 4 patients. The evolution was favorable in 3 of them. The fourth patient had a dramatic neurological outcome, though the delay between the onset of fever and diagnosis of meningitis was similar in all patients. No patient was immunosuppressed. But the patient who has had a dramatic outcome was born from HIV-infected mother. It is well described now that children born from HIV-infected mothers are at a high risk of developing bacterial infections.[9] Although *Salmonella* meningitis is rare in children, it remains a serious infection. Our study confirms the literature findings.[10] Early diagnosis and antibiotic treatment are necessary for a better therapeutic response and to prevent progression toward sequelae or death. A long-term effects monitoring for early developmental assessment for survivors is vital.

For all the 4 patients, a follow-up on psychomotor development with research of sensory disturbances was set up. We have noted no death among the 4 children and 1 patient had a severe neurologic outcome according to our monitoring.

### 5. Conclusion

*Salmonella* meningitis is rare in infant but is severe with a high risk of sequelae in survivors. Early diagnosis and treatment with combination of 3GC plus quinolones for a minimum of 3 weeks is necessary to avoid severe sequelae and death. The long-term monitoring for survivors is useful to improve the functional prognosis.

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