A previously healthy, 10-month-old male presented with new-onset seizure activity and fever of unknown origin (FUO) for 6 weeks. The child’s mother reported tonic-clonic movements that lasted for about 15 min. The seizure-like activity resolved with one dose of lorazepam given at the emergency department of an outside hospital. At the well-child clinic visit at 9 months of age, his primary physician noticed an increase in the patient’s head circumference above the 97th percentile. The child was referred for magnetic resonance imaging (MRI) of the brain, which showed a left-sided frontoparietal subdural fluid collection, approximately 12 mm in size, consistent with a subdural hematoma. Because the patient was asymptomatic without any neurologic deficit, there was no intervention. Three weeks later, a repeat MRI of the brain showed a stable appearance of the collection.

The patient’s mother stated that her son had recurrent fevers that started a few days after his 9-month well-child visit. The fever was initially low grade, at 100–101 °F for the first 2 weeks, then had increased to 103–104 °F during the previous 3 weeks, with minimal response to acetaminophen and ibuprofen. The mother also recalled that the infant had a small-to-moderate amount of intermittent, watery, and non-bloody diarrhea during the previous 3 weeks. This had been attributed to an antibiotic-related diarrhea associated with empiric treatment with amoxicillin. The patient was evaluated by many physicians, including in three emergency departments, and on multiple occasions for his prolonged fever. A diagnosis of viral upper respiratory infection was made twice and managed by acetaminophen. Acute otitis media was diagnosed on another occasion and managed by a course of amoxicillin. Physicians who treated the child did not feel that he required hospital admission during the 6-week illness prior to his presentation to our center.

The history was complicated because it was suspected that the subdural hematoma was a result of non-accidental trauma. His mother had reported that he fell off his bed and hit his head a few months before and that she was unaware of any additional head trauma. The Department of Children and Family Services was involved in the case. A skeletal survey and ophthalmology examination at the time of the initial trauma were normal.

On arrival to an outside hospital prior to transfer to our center, the mother denied any history of sick contacts or exposures to tuberculosis, pets, or other animals. However, additional history taken 2 days after admission revealed that the child had direct contact with his maternal grandmother’s two small turtles. Furthermore,
there was suspected exposure to chicken bones at a recent family barbecue. The patient’s mother worked as a food handler in a restaurant.

The patient was transferred to our tertiary care medical center’s pediatric emergency department. His initial vital signs were temperature 103 °F, pulse 174 beats per minute (normal range for age, 80–140), respiratory rate 35 breaths per minute (normal range for age, 20–30), and blood pressure 88/46 mmHg (normal range for age, 75–100/50–70). Once the seizure activity was aborted, no subsequent episodes were reported. The physical examination demonstrated fever, irritability, congestion, rhinorrhea, and macrocephaly. The anterior fontanelle was bulging but not tense. The patient was alert and had normal strength, and the rest of the physical examination was normal.

Computed tomography (CT) of the brain revealed a subacute cerebral convexity abnormality consistent with a subdural hematoma in the left frontoparietal region, as well as some acute hemorrhage with midline shift and mild subfalcine herniation. The previously identified subdural fluid collection had grown in size. The thickness of the collection had increased to approximately 30 mm compared with 14 mm 2 weeks before, and there was mass effect (Fig. 11.1). Initial laboratory studies were significant for leukocytosis with bandemia and an elevated C-reactive protein (Table 11.1). Further work-up in the setting of FUO including virologic studies was normal. A lumbar puncture could not be performed given the findings on the CT of the brain.

The differential diagnosis for the patient’s prolonged febrile illness was broad. Given fever for 6 weeks in the setting of a chronic subdural hematoma complicated by new-onset seizures, subdural empyema was considered likely. Other possible diagnoses are listed in Table 11.2.

The patient received parental antibiotics, including ceftriaxone and vancomycin, as empiric, broad spectrum coverage for meningitis. He was then transferred to the pediatric intensive care unit and underwent an emergent neurosurgical procedure to drain the fluid collection, which was described as a mixture of

![CT of the brain with contrast at the time of presentation showing a large left convexity abnormality consistent with a subacute subdural hematoma measuring 30 mm in greatest thickness and causing localized mass effect and minimal midline shift](image)

### Table 11.1 Laboratory results from admission

| Laboratory study                      | Result               |
|---------------------------------------|----------------------|
| Complete blood count                  |                      |
| WBC (per μL) (ref. 6000–17,300/μL)    | 18,000               |
| Neutrophils (%)                       | 60%                  |
| Lymphocytes (%)                       | 30%                  |
| Monocytes (%)                         | 7%                   |
| Hemoglobin (g/dL) (ref. 10.3–13.2 g/dL) | 7.7                 |
| Platelets (per μL) (ref. 150,000–450,000/μL) | 570,000              |
| C-reactive protein (mg/L) (ref. <3 mg/L) | 224                 |
| Complete metabolic panela             | Within normal limits |
| Blood culture                         | Negative             |
| Urinalysis                            | Normal               |
| Urine culture                         | Negative             |
| Respiratory viral panel (by polymerase chain reaction)b | Rhinovirus/enterovirus positive |

*aComplete metabolic panel includes glucose, calcium, albumin, total protein, electrolytes, blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and bilirubin
*bPathogens in the respiratory viral panel: adenovirus, coronavirus (229E, HKU, NL63, and OC43 subtypes), human metapneumovirus, rhinovirus/enterovirus, influenza A (H1 2009, H1, and H3 subtypes), influenza B, parainfluenza 1, respiratory syncytial virus, Bordetella pertussis, Chlamydia pneumoniae, and Mycoplasma pneumoniae
frank pus and blood. The fluid was sent for diagnostic studies. The cell count and other tests of the evacuated fluid analysis are shown in Table 11.3. The Gram stain showed Gram-negative bacilli (Fig. 11.2), and the bacterial culture grew *Salmonella* Sandiego (Table 11.3). The case was reported to the state Department of Public Health.

Further imaging was performed to rule out another focus of *Salmonella* infection, including chest X-ray, echocardiogram, and abdominal ultrasound, which were normal. Given that *Salmonella* superinfection of a subdural empyema is a rare extraintestinal manifestation of *Salmonella* infections, the presentation was concerning for a primary immunodeficiency.

### Table 11.2  Differential diagnosis of a child with fever, seizures, and a subdural hematoma

| Subdural empyema or infective subdural hematoma |
|------------------------------------------------|
| • Gram-positive bacteria                      |
|   • Coagulase-negative *Staphylococcus*       |
|   • *Staphylococcus aureus*                   |
|   • *Streptococcus* spp. (including *S. pneumoniae*) |
| • Gram-negative bacteria                      |
|   • *Haemophilus influenzae*                  |
|   • Klebsiella spp.                           |
|   • *Escherichia coli*                        |
|   • *Salmonella* spp.                         |
| • Mycobacteria                                |
| • Fungi (including *Candida* spp.)            |
| Meningitis                                    |
| • Bacterial                                   |
| • Fungal                                      |
| • Tuberculous (*Mycobacterium tuberculosis*)  |
| Encephalitis                                  |
| • Herpes simplex virus (HSV)                  |
| • Enteroviruses, including Coxsackievirus and echovirus |
| • Human herpes virus-6 (HHV-6)                |
| *Shigella* infection with neurologic complications |
| Febrile seizure                               |
| Malignancy                                    |
| • Brain tumors                                |
| • Infantile leukemia                          |
| Metabolic                                     |
| • Glutaric aciduria type 1                    |
| Genetic epilepsies with febrile seizures      |

11.1 Work-Up for Primary Immunodeficiency

The Immunology Service was consulted, and the assessment for an immunologic disorder in our patient was negative (Table 11.4). Measurement of immunoglobulin G (IgG) is useful in cases of suspected antibody deficiency. Measurement of immunoglobulin E (IgE) is useful in a patient with recurrent bacterial infections and dermatitis because if the level is greater than 2000 IU/mL, hyperimmunoglobulin E syndrome is suspected. Measurement of IgG antibody titers to tetanus, diphtheria, *Haemophilus influenzae* type B, and protein-conjugated pneumococcal vaccines is used to assess response to protein antigens, which is critical to assess the integrity of humoral immunity. The mitogen lymphocyte proliferation test is used to evaluate the integrity of T-cell responses to plant mitogens phytohemagglutinin (PHA) and pokeweed mitogen (PMW), which are powerful stimulants of T cells.

Lymphocyte subset analysis by flow cytometry is also an essential tool in the diagnosis of primary immunodeficiencies. Flow cytometry enables qualitative and quantitative enumeration of lymphocyte subsets, including CD4+ and CD8+ T cells, B cells, and natural killer (NK) cells. This test is important in determining if there are defects in T-cell numbers (as in severe combined immunodeficiency [SCID] or DiGeorge syndrome) or defects in T-cell function (as in common variable immunodeficiency [CVID]). The dihydrorhodamine (DHR) flow cytometry test is sent to evaluate for chronic granulomatous disease (CGD), primarily a defect in neutrophil function, with reduced ability to produce a respiratory burst for pathogen killing.

### 11.2 Salmonellosis

Our final diagnosis was *Salmonella enterica* serovar Sandiego superinfection of a left-sided subdural hematoma. The most likely source of the infection was enteritis, which presumably led to bacteremia with seeding of the hematoma. Blood cultures, interestingly, showed no growth. The
The patient was treated with intravenous (IV) ceftriaxone for 6 weeks. He defervesced a few days after the evacuation of the subdural empyema. He was discharged without neurologic complications.

*Salmonella* are Gram-negative bacilli that belong to the family *Enterobacteriaceae*. More than 2500 *Salmonella* serovars have been described; most serovars causing human disease are classified within O serogroups A through E. Species and subspecies are distinguished using biochemical reactions. There are only two recognized species, *Salmonella enterica* and *Salmonella bongori* [1].

---

**Table 11.3** Laboratory results on fluid drained from subdural space

| Test (normal range for CSF)                  | Result          |
|---------------------------------------------|-----------------|
| Total cell count (0–30/μL)                 | 196,750 (H)     |
| WBC (0–30/μL)                               | 154,500 (H)     |
| RBC (0/μL)                                 | 42,250 (H)      |
| Neutrophils (0–6%)                          | 98% (H)         |
| Eosinophils (0%)                            | 0%              |
| Lymphocytes (40–80%)                        | 1% (L)          |
| Monocytes (15–45%)                          | 1% (L)          |
| Basophils (0%)                              | 0%              |
| Plasma cells (0%)                           | 0%              |
| Unclassified cells (0%)                     | 0%              |
| Protein (60–90 mg/dL)                       | 2142            |
| Glucose (50–70 mg/dL)                       | <20             |
| Gram stain                                 | Gram-negative bacilli |
| Culture result                              | *Salmonella* spp. |
| Serotype                                    | *Salmonella* Sandiego |
| Antimicrobials: susceptible to              | Ceftazidine, ceftriaxone, trimethoprim/sulfamethoxazole, and ampicillin |

---

**Figure 11.2** Gram stain morphology from fluid drained from subdural space showing Gram-negative bacilli, specified to *Salmonella*

---

**Table 11.4** Immunology work-up

| Test (normal range for CSF)                  | Result          |
|---------------------------------------------|-----------------|
| Lymphocyte subset 3 (quantifies T cells), blood | Normal         |
| Quantitative immunoglobulins and Total IgE, serum | Normal         |
| Mitogen proliferation test                  | Normal          |
| Tetanus toxoid IgG, serum                   | Positive and appropriately responded to vaccination history |
| Diphtheria toxoid IgG, serum                 | Positive and appropriately responded to vaccination history |
| Pneumococcal IgG, serum                      | Partial immunity consistent with incomplete vaccination course; appropriate given patient’s age and immunization history |
| *Haemophilus influenzae* type B IgG, serum   | Normal          |
| Isohemagglutinins Anti-A, Anti-B, serum      | Normal          |
| Dihydrorhodamine 123 test flow cytometry     | Normal          |
| Absolute CD4+ T cells, blood (normal range, 1400–4300/μL) | 1544.78         |
| Absolute CD3+ T cells, blood (normal range, 1900–5900/μL) | 2688.54         |
| Ratio CD4:CD8 (normal range, 1.3–4.7)        | 2.0             |
Nontyphoidal *Salmonella* organisms are among the most common causes of laboratory-confirmed cases of enteric infection. The principal reservoirs for these organisms are birds, mammals, reptiles, and amphibians. However, some African serotypes that cause invasive human disease may have a human reservoir. In industrialized countries, the major food sources of transmission to humans are poultry, beef, eggs, and dairy products. Many other foods, such as fruits, vegetables, peanut butter, frozen pot pies, powdered infant formula, cereal, and bakery products, have been implicated in outbreaks in the United States (US) and Europe [1, 2]. Turtles with a shell length of <4 in. are a well-known carrier of *Salmonella* species that can cause human infections. *Salmonella* Sandiego was isolated from most ill patients in one case series of infections linked to small turtles [3].

Unlike nontyphoidal *Salmonella* serovars, the enteric fever serovars (*Salmonella* serovars Typhi, Paratyphi A and Paratyphi B) are uncommon in the USA. They can cause a protracted bacteremic illness known as typhoid (*Salmonella* Typhi) and paratyphoid (*Salmonella* Paratyphi A or B), and they are collectively called enteric fevers [1, 2]. They are restricted to human hosts and cause both clinical and subclinical infections. Chronic human carriers, usually involving infection of the gallbladder and occasionally the urinary tract, constitute the primary reservoir in areas with endemic infection, well known from the historical figure of Typhoid Mary.

The incidence of nontyphoidal *Salmonella* infection is highest in children <4 years of age. In the USA, rates of invasive infections and mortality are highest in infants, the elderly, people with hemoglobinopathies, and immunocompromised hosts. The incubation period for nontyphoidal *Salmonella* gastroenteritis usually is 12–36 h (range, 6–72 h). For enteric fever, the typical incubation period is 7–14 days (range, 3–60 days) [1, 2].

Nontyphoidal *Salmonella* organisms cause a spectrum of illness ranging from asymptomatic gastrointestinal tract carriage to gastroenteritis and bacteremia. Focal infections, such as meningitis, brain abscess, and osteomyelitis, may be diagnosed even in the absence of documented bacteraemia. Gastroenteritis is the most common illness associated with nontyphoidal *Salmonella* infection, most often resulting in symptoms of diarrhea, fever, and abdominal cramps. Isolation of *Salmonella* from stool, blood, urine, bile, and/or cultured material from a focus of infection is diagnostic. Gastroenteritis is diagnosed by stool culture. Diagnostic tests to detect *Salmonella* antigens by enzyme immunoassay, latex agglutination, and monoclonal antibodies have been developed. Commercial immunoassays may also be used to detect antibodies to enteric fever serovars [1, 2], but the tests have limited sensitivity and specificity [4].

Antimicrobial therapy is not indicated for most patients with asymptomatic infection or uncomplicated gastroenteritis caused by nontyphoidal *Salmonella* serovars. Therapy does not shorten the duration of diarrheal disease and can even prolong the duration of fecal excretion of the pathogen. Although of unproven benefit, antimicrobial therapy is recommended for gastroenteritis caused by nontyphoidal *Salmonella* serovars in people at increased risk of invasive disease. This includes infants <3 months of age and people with chronic gastrointestinal tract disease, cancer, hemoglobinopathies, human immunodeficiency virus (HIV) infection, or other immunosuppressive illnesses or therapies [1, 2]. If antimicrobial therapy is initiated in patients with gastroenteritis, amoxicillin or trimethoprim-sulfamethoxazole (TMP-SMX) may be used for susceptible strains. Resistance to these agents is becoming increasingly common, especially in resource-limited countries. In cases of resistance, a fluoroquinolone or azithromycin is usually an effective substitute. For HIV-infected patients with localized invasive disease or bacteremia, empiric therapy with IV ceftriaxone is recommended. Once antimicrobial susceptibilities are available, ampicillin or ceftriaxone for susceptible strains is recommended.

Empiric treatment of enteric fever with ceftriaxone or a fluoroquinolone is recommended, and azithromycin may be an effective alternative. Once antimicrobial susceptibility results are known, therapy should be changed as necessary.
Corticosteroids may be beneficial in patients with severe enteric fever, which can lead to delirium, obtundation, coma, or shock [1, 2].

Typhoid vaccine is usually used in people at high risk of infection with *Salmonella* serovar Typhi. Two typhoid vaccines are licensed for use in the USA: a Vi capsular polysaccharide vaccine for parenteral use and an oral live-attenuated vaccine. Neither one provides complete protection. The vaccine efficacy appears high in US travelers [5]. However, the vaccines are not nearly as effective in populations where typhoid is endemic [6]. Efficacy at 1 and 2 years was 35% and 58% for the oral vaccine and 69% and 59% for the intramuscular vaccine, respectively [7]. Immunization is recommended only for specific populations, including travelers to areas where risk of exposure is recognized; people with intimate exposure to a documented typhoid fever carrier, as occurs with prolonged household contact; laboratory workers having frequent contact with *Salmonella* serovar Typhi; and people living outside the USA in areas with endemic typhoid infection [1, 2].

**Key Points/Pearls**

- Nontyphoidal *Salmonella* infections are far more common in the USA than typhoid fever.
- Populations at particular risk for invasive disease include infants <3 months of age and people with chronic gastrointestinal disease, cancer, hemoglobinopathies, HIV infection, or other immunosuppressive illnesses or therapies.
- The principal reservoirs for nontyphoidal *Salmonella* include birds, mammals, reptiles, small turtles, and amphibians; a thorough review of exposure history may reveal clues that can help to narrow the differential diagnosis.
- Nontyphoidal *Salmonella* cause asymptomatic gastrointestinal tract carriage, gastroenteritis, bacteremia, and focal infections including meningitis, brain abscess, and osteomyelitis.
- Superinfection of a subdural empyema should be considered in a child with chronic subdural hematoma and the clinical triad of prolonged fever, gastroenteritis, and neurological abnormalities.
- *Salmonella* Sandiego, a rare nontyphoidal *Salmonella* serotype, has been implicated in a number of US outbreaks linked to contact with small turtles.
- Antibiotics usually are not indicated for patients with either asymptomatic nontyphoidal *Salmonella* infection or uncomplicated gastroenteritis; they are usually recommended only in certain populations at high risk for invasive disease.
- Typhoid vaccines are recommended and considered highly effective in travelers to countries where typhoid is endemic.
- The live typhoid vaccine is contraindicated in immunocompromised patients.
- Prolonged nontyphoidal *Salmonella* bacteraemia may be due to an aortic mycotic aneurism, a life-threatening condition that requires vascular surgery interventions.

**References**

1. American Academy of Pediatrics. *Salmonella* infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red book: 2015 Report of the Committee on Infectious Diseases. 30th ed. Elk Grove Village: American Academy of Pediatrics; 2015. p. 695.
2. Pegues DA, Miller SI. *Salmonella* species, including *Salmonella* Typhi. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett’s principles and practice of infectious diseases, vol. 2. 7th ed. Philadelphia: Elsevier; 2010. p. 2887.
3. United States Centers for Disease Control and Prevention. National enteric disease surveillance: four multistate outbreaks of human *Salmonella* infections linked to small turtles. [http://www.cdc.gov/salmonella/small-turtles-10-15/index.html](http://www.cdc.gov/salmonella/small-turtles-10-15/index.html). Posted May 18, 2016. Accessed 22 June 2017.
4. Siba V, Horwood P, Vanuga K, et al. Evaluation of serological diagnostic tests for typhoid fever in Papua New Guinea using a composite reference standard. Clin Vaccine Immunol. 2012;19(11):1833–7.
5. Mahon BE, Newton AE, Mintz ED. Effectiveness of typhoid vaccination in US travelers. Vaccine. 2014;32:3577–9.
6. Jackson B, Iqbal S, Mahon B. Updated recommendations for the use of typhoid vaccine—advisory committee on immunization practices, United States, 2015. MMWR. 2015;64(11):305–8.
7. Tabarani CM, Bennett NJ, Kiska DL, Riddell SW, Botash AS, Domachowske JB. Empyema of preexisting subdural hemorrhage caused by a rare *Salmonella* species after exposure to bearded dragons in a foster home. J Pediatr. 2010;156(2):322–3.