FEVER OF UNKNOWN ORIGIN IN A FAMILY DUE TO SALMONELLA TYPHI: A CASE REPORT

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Abstract: We report a family of 4 siblings who presented with fever of unknown origin over a period of 2 months. Salmonella typhi was eventually isolated from one sibling. All 4 cases were treated at University Teaching Hospital of Kigali; 3 in the Department of Pediatrics and one in Internal Medicine, in 2014.

CASE PRESENTATION

Patient 1

The index case (patient 1) was a 12-year-old girl admitted for intermittent fever of one month's duration. The main complaints were generalized body weakness, headache, body sweats, joint pain, vomiting, and abdominal pain that began 3 weeks prior admission. She also reported a 5kg weight loss. She had been treated as an outpatient with Cimetidine and Acetaminophen with no improvement. There were no known tuberculosis exposures; the mother reported the presence of ticks, rats, and bedbugs in the home. She drank tap water that was not always boiled. She lived with 4 siblings and her mother; four children slept in the same bedroom sharing the same mattresses. The mother and the youngest sibling were HIV positive on ART.

On admission, the child was ill looking and weak. Vital signs were temperature of 38.8oC, heart rate of 88 beats/min, blood pressure 100/60 mmHg, respiratory rate 20/min, and SpO2 98% on room air. Physical examination was significant for mild peri-umbilical tenderness, and moderate tenderness on passive mobilization of lower limbs especially at the ankles.

Initial work-up revealed leukopenia, thrombocytopenia, microcytic anemia, elevated transaminases, elevated amylase, hyponatremia, and elevated ESR (Table 1). Urinalysis was normal, blood smear for malaria was negative, and HIV serology test (ELISA) was negative. Initial blood cultures were negative. Stool microscopy revealed Entamoeba coli cysts. After 2 weeks of negative work-up and persistent fever, the decision was made to give her an empiric course of doxycycline to empirically treat possible rickettsial infection, rat bite fever, or brucellosis. After defervescing for several days, she was discharged to complete a 14-day course of doxycycline with close follow-up at outpatient department in one week. However she was readmitted one week later, at which time another blood culture was sent which grew Salmonella typhi on the second day of admission, sensitive to Ceftriaxone, and she was started on IV ceftriaxone.

At the time of patient 1's readmission, her 14 year old sister (patient 2) and 8 year old brother (patient 3) were also admitted with similar symptoms.

Patient 2

This was the 14-year-old sister of patient 1, who complained of symptoms of one month's duration: intermittent knee and ankle pain, headache, abdominal pain, sore throat. She was seen in outpatient clinic 17 days prior to admission and treated for tonsillitis with Amoxicillin 1g twice a day for 7 days, Paracetamol 500mg three times a day alternating with Ibuprofen 400mg three times day for 5 days, but the fever persisted. Ten days after this treatment, she developed post-prandial vomiting, dizziness, chills and periumbilical abdominal pain. She also reported some episodes of watery stools, weight loss and decreased appetite.

On physical exam, the child was weak and obtunded. She had temperatures of 37.8-40.10 C, heart rate 98 beats/min, respiratory rate 24 breaths/min, and SpO2 98% on room air. There was diffuse abdominal tenderness (more pronounced in the peri-umbilical area), and muscle power was reduced to 4/5 in all limbs with bilateral ankle clonus. The rest of the physical exam is normal. Lab testing revealed leukopenia, elevated transaminases, and hyponatremia (Table 1). Also negative were HIV ELISA, blood smear for malaria, and serologies for HBV and HCV. Blood cultures have been negative. Parents refused to give consent for lumbar puncture.

Patient 3

This is an 8-year old boy who presented with a history similar to patient 1 and 2 (fever of unknown origin). Unfortunately, his medical file could not be found to give a complete review of his history and physical exam.

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Table 1. Laboratory results of Patients 1 and 2

	Patient 1			Patient 2						
	05/6/2014	28/6/2014	19/7/2014	05/6/2014	09/6/2014	10/6/2014	11/6/2014	12/6/2014	16/6/2014	20/6/2014
WBC (...10^9/l)	3.8	7.8	4.1	2.6						
Neutrophils (%)	59.3	61.8	48	74.6						
Lymphocytes (%)	36.9	33.3	48.8	22.9						
Mixed (%)	-	4.9	13.4	2.5						
Platelets (...10^9/l)	52	389	204	121						
MCV (fl)	76.5	82	80.4	77.6						
MCH (pg)	26.1	27.6	27.7	27.1						
Hemoglobin (g/dl)	9.2	10.5	12.4	12.2						
Hematocrit (%)	34.1	31.2	36	35						
Urea (mmol/l)	4.49	2.53		-		27.13	26.64	21.3	5.65	
Creatinine (micromol/l)	63.1	39.1		255.4	335.4	257.1	198.6	139.7	58	
Albumin	29.08			34.66						
ASAT (IU/l)	627.5			337.7		354.5			56.9	
ALAT (IU/l)	118.8			116.2		144.4			48.1	
Sodium (mmol/l)	123	134.2		123.4	135.3	143.8		145.1	137.8	133.1
Potassium (mmol/l)	3.1	3.23		2.65	2.47	2.51		2.46	2.84	4.91
Chloride (mmol/l)	86.9	97.6		88.4	102.4	107.4		107.8	99.9	97
Amylase	498.6									
HIV- ELISA	Negative			Negative						

MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, WBC: White Blood Cell, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, HIV: Human Immune Deficient Virus, ELISA: Enzyme-Linked Immunosorbent Assay, LDH: Lactate Dehydrogenase.

Evolution of cases

The presentation of 3 siblings with undifferentiated fever with negative laboratory testing, plus report of a 4th sibling sick at home, prompted the clinical team to call the outbreak investigation team from the National Reference Laboratory (NRL). Samples including blood cultures, serology for Louse-borne relapsing fever (Borrelia), Trench fever (Bartonella Quintana), Rickettsioses, Brucellosis, Leptospirosis, Arthropod-borne viral fevers, Salmonella typhi, tick bite disease, Rat bite fever; as well as bed bugs from the home were taken and sent for analysis at NRL and the Centers for Disease Control (CDC) in Atlanta, GA, USA.

Patient 1's blood culture grew Salmonella typhi on the second day of the second admission. The isolate was sensitive to all tested antibiotics: Cefotaxime, Gentamicin, Chloramphenicol, Nalidixic acid, Imipenem, and Ceftriaxone. After starting IV ceftriaxone, the liver and renal function tests and electrolytes normalized after 6 days. Fever subsided after 7 days of antibiotics. She was discharged after 15 days on oral Cefixime for 7 days, with appointment in the outpatient clinic for follow-up in one week.

The other siblings (sisters: 14 (patient 2) and 17 years old, and brother of 8 years (patient 3)) were treated with IV ceftriaxone for possible S. typhi, and oral Doxycycline for possible zoonotic infections while lab results from NRL and the CDC were pending.

Testing done at NRL and the CDC did not yield any positive results besides the blood culture from patient 1 that was confirmed to be positive for Salmonella typhi with susceptibility to Ceftriaxone.

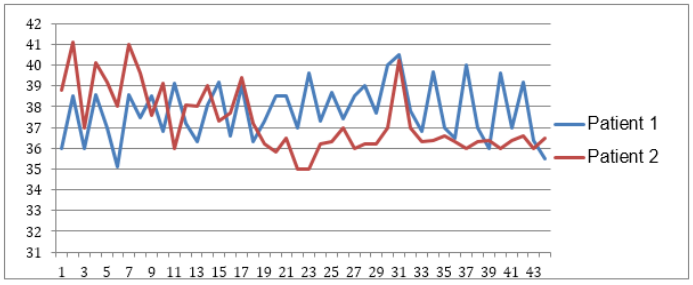

Figure1. Temperature patterns of patients during hospitalization.

With the given clinical scenario and investigation results, we surmise that the cause of the febrile illnesses of this family was most likely due to Salmonella typhi infection within an overcrowded household with poor hygienic conditions.

DISCUSSION

According to World Health Organization (WHO), typhoid fever can be an issue in areas with overcrowding and poor hygiene (World Health Organization, 2003). It is caused by Salmonella typhi, a gram-negative bacillus. Transmission is oral-fecal, usually by ingestion of contaminated food and/or water. Once the microbe reaches the small intestines, it penetrates the mucosal epithelium via microfold cells or enterocytes. In the lamina propria it triggers the influx of macrophages, which ingest microbe but generally do not kill the bacteria. The microbe multiplies within the mononuclear phagocyte, and then is released into the bloodstream (Singh, 2001).

Generally the incubation period ranges between 3 to 60 days with an average of 8 to 14 days. This period depends on the quantity of inoculum and host factors (World Health Organization, 2003).

The clinical presentation of typhoid fever can be nonspecific ranging from mild symptoms (such as low grade fever, malaise, headache, and dry cough), to severe abdominal pain, intestinal perforation and neurologic manifestations (Raffatellu, Wilson, Winter, & Baumler, 2008). It can therefore resemble other diseases that are common in areas where typhoid fever is endemic, such as malaria, pneumonia, and tuberculosis.

Diagnosis in resource-limited settings can be a challenge due to lack of access to laboratory facilities, and also because the presenting symptoms can be nonspecific. The gold standard for diagnosis is bone marrow culture (Darton, Blohmke, & Pollard, 2014; World Health Organization, 2003). Blood cultures have lower sensitivity due to low numbers of bacteria present in blood at the presentation of symptoms. In addition the culture yield decreases with the longer duration of illness (Darton et al., 2014). Stool cultures can be positive in about one-third of cases but frequently are negative by the time symptomatic patients seek medical attention. The Widal test is a serologic test that detects antibodies to S. typhi, but it requires paired acute and convalescent serum samples to detect a minimum four-fold increase in titers to be considered positive. Rapid diagnostic tests are limited by a high rate of false positivity and low specificity due to nonspecific binding of antigens to antibodies. Deoxyribonucleic acid polymerase chain reaction (DNA PCR) has also been used for diagnosis, but is limited by low concentrations of microbial DNA in clinical samples (Waddington, Darton, & Pollard, 2014).

Treatment of typhoid fever consists of antibiotics, mostly fluoroquinolones or cephalosporins (according to antibiotic susceptibility), antipyretics, and individualized supportive therapy based on the patient's presentation. The complications of typhoid fever have to be managed specifically and early to avoid possible permanent sequelae (Singla, Bansal, Gupta, & Chander, 2013; World Health Organization, 2003).

Typhoid fever can be prevented by availability of clean water, proper sanitation, and education of food safety practices, and where it is applicable, vaccination of risky populations (Darton et al., 2014; Iseri, Bayraktar, Akta, & Durmaz, 2009; Raffatellu et al., 2008; Singla et al., 2013; Waddington et al., 2014; World Health Organization, 2003).

In our cases, the diagnostic work-up of undifferentiated fever in a family was challenging due to the initial negative blood cultures in the index case, plus initial lack of access to serologic testing for zoonotic infections for which the patient had the risk factors as ascertained by history.

Globally, typhoid fever is a public health problem whose real impact is difficult to measure because it shares clinical manifestations with other diseases that are common in endemic areas. In endemic areas and regions with large outbreaks, most cases appear to be aged between 3 and 19 years (World Health Organization, 2003).

CONCLUSION

Salmonella typhi infection remains a public health problem especially in developing countries. It can present as an isolated case, or as in our report, as an outbreak particularly in overcrowded areas with poor hygiene conditions. It should be considered in a patient with fever of unknown origin from an endemic area, even when microbial cultures are negative.

REFERENCES

1. Darton, T. C., Blohmke, C. J., & Pollard, A. J. (2014). Typhoid epidemiology, diagnostics and the human challenge model. Current Opinion in Gastroenterology, 30(1), 7–17.

2. Iseri, L., Bayraktar, M. R., Akta, E., & Durmaz, R. (2009). Investigation of an Outbreak of Salmonella Typhi in Battalgazi District, Malatya-Turkey. Brazilian Journal of Microbiology, 40, 170–173.

3. Raffatellu, M., Wilson, R. P., Winter, S. E., & Baumler, A. J. (2008). Clinical pathogenesis of typhoid fever. Journal of Infection in Developing Countries, 2(4), 260–266.

4. Singh, S. (2001). Typhoid Fever: Pathogenesis and Laboratory Diagnosis. Journal, Indian Academy of Clinical Medicine, 2(1 and 2), 17–20.

5. Singla, N., Bansal, N., Gupta, V., & Chander, J. (2013). Outbreak of Salmonella Typhi enteric fever in sub-urban area of North India: a public health perspective. Asian Pacific Journal of Tropical Medicine, 6(2), 167–8.

6. Waddington, C. S., Darton, T. C., & Pollard, A. J. (2014). The challenge of enteric fever. Journal of Infection, 68(SUPPL1), S38–S50.

7. World Health Organization. (2003). Background document: The diagnosis, treatment and prevention of typhoid fever. Retrieved from http://apps.who.int/iris/bitstream/10665/68122/1/WHO_V-B_03.07_eng.pdf