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Case Report

Paediatrics Section

Enteric Fever in Two Siblings with Severe Haemorrhage and Shock

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ABSTRACT

Enteric fever is an infectious disease caused by *Salmonella typhi*, more common in developing countries. It can affect almost all organ systems of the body. There have been occasional reports in literature of patients with enteric fever presenting with severe haemorrhage and very rarely both haemorrhage and shock. Here, we report cases of two siblings, both of them suffering from enteric fever simultaneously, presenting with severe multiple site haemorrhage, shock and with severe thrombocytopenia. The elder sibling presented with encephalopathy as well. Both siblings survived after receiving appropriate platelet and blood transfusions alongside ionotropes and appropriate antibiotics.

Keywords: Encephalopathy, Gastrointestinal haemorrhage, Petechiae, Thrombocytopenia

CASE REPORT

A 11-year-old male (sibling 1) was admitted to the hospital with complains of fever for eight days and decreased oral acceptance for five days. He also complained of abdominal pain, vomiting and skin rashes on face and extremities for the last three days. The patient was being treated at home with some oral medications (details of which is not available) prior to admission to this hospital. At presentation, patient was febrile and toxic looking. His heart rate was 100 beats/minute, respiratory rate was 24 breaths/minute, pulse was low volume and blood pressure was 60/40 mmHg. There were multiple petechial rashes over face and extremities. On abdominal examination, his liver was 4.5 cm below the costal margin (liver span was 12 cm) and spleen 3 cm below the costal margin. The differential diagnosis could include dengue with shock or complicated enteric fever or complicated malaria depending upon the presentation. The patient was given normal saline boluses (3 boluses of 20 mL/kg intravenously) and antibiotic ceftriaxone (100 mg/kg/day intravenously) (third-generation cephalosporin) with antimalarial artesunate along with supportive therapy. Shock did not improve despite the normal saline boluses, so inotropes were started (dopamine injected at 10 microgram/kg/min). Investigations like blood culture, widal, peripheral smear for malarial parasite and dengue serology were sent to look for aetiology. The haemogram showed Hb 9.4 gm/dL, Total Leukocyte Count (TLC) 5600/cumm of blood and platelet count 250x10^3/cumm. Coagulation profile was normal. All the investigation reports are depicted in tabular form [Table/Fig-1]. On Day two of admission, the patient developed an altered sensorium. On Day three, shock persisted and platelet count started to fall. On Day four, the patient developed melena and haematuria with a platelet count of 40,000/cu mm and Hb was 7 gm/dL, thus, platelet and Packed Red Blood Cell (PRBC) transfusion given. On the fifth day, the patient developed nasal bleeding and nasal packing was done to counter it. After stabilisation, dopamine therapy was stopped. Meanwhile, investigation reports showed a positive culture of *Salmonella typhi* sensitive to ceftriaxone, azithromycin and ciprofloxacin. On Day six of admission, oral azithromycin

Investigation	Day 2	Day 3	Day 4	Day 5	Day 6	Day 9	Day 13
Haemoglobin (gm/dL)	9.4	7.8	7.0	9.2	10.7	8.8	9
TLC (/cumm)	5600	6800	11900	8800	10800	14100	15000
Platelet count (/cumm)	250000	51000	40000	45000	40000	226000	230000
Serum Urea (mg/dL)	35		22				
Serum Creatinine (mg/dL)	0.8		0.8				
Sodium (mg/dL)	145		147		138		140
Potassium (mg/dL)	5.2		4.8		5.0		5.2
INR		1.32		1.5	1.3	1.1	
Total bilirubin (mg/dL)		1.0					
SGOT/SGPT (U/L)		24/26					
ALP (U/L)		108					
Serum Albumin (gm/dL)		4.4					
Serum globulin (gm/dL)		3.2					
Widal test		Negative			Positive To and Th 1:160		
Blood Culture			Salmonella typhi +				
Chest X Ray		NAD					
USG abdomen		NAD					

[Table/Fig-1]: Findings depicting the investigation reports of the index case (sibling1).
INR- International normalized ratio NAD- No abnormality detected

was added in view of persistence of fever and to cover resistant salmonella strains. Antibiotic therapy with antibiotic ceftriaxone (100 mg/kg/day intravenously) and azithromycin (20 mg/kg/day orally) was continued. On Day eight, the patient became afebrile. Vitals of the patient including temperature, blood pressure, pulse rate and respiratory rate have been depicted in tabular form [Table/Fig-2]. The patient was discharged after 13 days of admission, completely asymptomatic.

An 8-year-old female (sibling 2) was admitted with complaints of fever, pain in abdomen, petechiae over face, headache and generalized bodyache for 15 days. She was febrile and toxic looking. Her heart rate was 108 beats/minute, respiratory rate was 28 breaths/ minute, pulse were weakly palpable and blood pressure was 70/54 mmHg. She was also in shock with multiple petechial rashes over her face. On abdominal examination, she also had hepatosplenomegaly with the liver 3 cm palpable below costal margin (liver span was 10 cm) and spleen 2 cm palpable below costal margin. A probable diagnosis of complicated enteric fever was kept in view of similar presentation

Date/ Day of Admission	Time	Temperature (°F)	Heart rate (per minute)	Respiratory rate (per minute)	BP (mmHg)	Comments
Day 1	On admission 11:45 pm	103	100	24	60/40	Bolus given normal saline bolus (20 mL/ kg intravenously)
Day 2	9 am	102.5	98	24	78/60	Bolus given normal saline bolus (20 mL/ kg intravenously)
	12pm	100.2	90	26	70/50	Dopamine started
	6 pm	99	90	22	100/70	Developed encephalopathy
Day 3	9 am	98.5	98	24	80/70	Bolus given normal saline bolus (20 mL/ kg intravenously)
	6 pm	101.2	110	26	110/76	
Day 4	9 am	98	96	22	108/74	PRBC and Platelet transfusion given for bleeding and platelet count 40×10^3 cu mm
	6 pm	96.5	94	22		
Day 5	9 am	102	100	22	92/60	Nasal bleed so nasal packing done
	6 pm	100	108	26	100/76	Dopamine stopped
Day 6	9 am	99.4	110	24	104/70	
	6 pm	101.4	120	26	102/66	Tab. Azithromycin (20 mg/kg/day orally) added in view of fever persistence
Day 7	9 am	100.8	102	28	110/70	
Day 8	9 am	96.5	86	22	110/76	Afebrile onwards

[Table/Fig-2]: Findings depicting the vitals of the index case (sibling 1) and actions taken.
PRBC- Packed red blood cells.

Investigation	Day 1	Day 2	Day 3	Day 9
Haemoglobin (gm/dL)	9.5	8.5	9.9	8.7
TLC (/cumm)	5100	4600	6200	4700
Platelet count (/c umm)	165000	263000	285000	247000
Serum Urea (mg/dL)	22		20	
Serum Creatinine (mg/dL)	0.8		0.9	
Sodium (mg/dL)	136		135	
Potassium (mg/dL)	3.4		3.8	
INR	1.2		1.0	
Total bilirubin (mg/dL)	1.2			
SGOT/SGPT (U/L)	38/36			
ALP (U/L)	128			
Serum Albumin (gm/dL)	4.0			
Serum globulin (gm/dL)	2.9			
Widal test		To, Th 1:160		
Blood Culture			Negative	
Chest X Ray		NAD		
USG abdomen		NAD		

[Table/Fig-3]: Table depicting the investigation reports of the younger sibling (sibling 2).
NAD- No abnormality detected

Date/ Day of Admission	Time	Temperature (°F)	Heart rate (per minute)	Respiratory rate (per minute)	BP (mmHg)	Comment
Day 1	On admission (10:00 pm)	100	108	28	70/54	Fluid boluses given (3 boluses of normal saline 20 ml/kg/day), inotrope started
Day 2	9:00 am	102	120	30	80/20	Dopamine continued
	6:00 pm	99	100	24	96/70	
Day 3	9:00 am	99.9	80	28	90/60	Dopamine tapered and stopped
	6:00 pm	101	98	26	90/70	
Day 4	9:00 am	98	90	24	100/60	Afebrile

[Table/Fig-4]: Findings depicting the vitals of the younger sibling (sibling 2) and actions taken.

as that of the other sibling. Shock was managed with fluids and inotropes. All the investigations of sibling 2 are depicted in tabular form [Table/Fig-3]. Vitals of the patient included temperature, blood pressure, pulse rate and respiratory rate which have been depicted in tabular form [Table/Fig-4]. Meanwhile, investigations were sent (blood culture, widal, peripheral smear for malarial parasite, dengue serology), haemogram showed Hb 9.5 gm/dL, TLC was 5100/cumm and platelet count 165x10^3/ cumm. Although, blood culture was sterile in this patient but widal was positive with TO and TH titers >1:160. On the fourth day of admission, patient became afebrile and was discharged after nine days of admission.

DISCUSSION

Typhoid fever is caused by a Gram negative bacterium *Salmonella typhi*. A similar but less severe disease is caused by *S. paratyphi A* followed by *S. paratyphi B* and *S. paratyphi C*. The most common mode of infection is contaminated water or food. Sewage contamination of water supply and person to person transmission through poor hygiene are important sources of infection. A classic presentation of slow, step ladder rise in fever and toxicity is rarely seen these days due to early antibiotic treatment. However, increased severity of illness and related complications are seen due to rising anti-microbial resistance. Severity of illness and clinical outcome of disease depends on many factors like duration of illness before starting treatment, antimicrobial used, vaccination history, virulence of strain, quantity of inoculum ingested, several host factors like age and immune status [1]. Enteric fever is more common in developing countries as compared to developed countries due to poor living conditions and sanitation [2].

Enteric fever can cause complications in any organ system of body [3]. According to a study done by Daoud AS et al., typhoid complications of bowel perforation, haemorrhage or septic shock were present in 5% patients [4]. Intestinal haemorrhage (<1%) and perforation (0.5-1%) are rare complications among children [5]. In the present report, elder sibling had gastrointestinal haemorrhage in the form of melena. He also had haematuria. As seen in the elder sibling, life-threatening complications in enteric fever generally occur after 2 to 3 weeks of illness and may include intestinal haemorrhage or perforation. In the present case, the patient (elder sibling) had encephalopathy due to typhoid fever although, it is a rare presentation but similar cases have been reported in literature with encephalomyelitis and other neurological manifestations like typhoid meningitis, Guillain-Barre syndrome, cranial or peripheral neuritis, and psychotic symptoms [6]. Other life threatening complications are myocarditis, pneumonia, disseminated intravascular coagulation, thrombocytopenia and haemolytic uremic syndrome [6].

In the present report, petechiae was present due to thrombocytopenia in both siblings. In a study done by Bhatnagar SK et al., various causes of pancytopenia were listed, of them infections were an important cause [7]. In his study of 23 (21%) patients with infections, enteric fever accounted for seven (30%) patients. Various mechanisms contribute to pancytopenia in enteric fever. Bone marrow undergoes histiocytic hyperplasia with haemophagocytosis or necrosis. Immune mediated haemolysis, hypersplenism and transient disseminated intravascular haemolysis are other mechanisms [8].

In a study done by Malik AS, out of 159 children with enteric fever 26% cases had thrombocytopenia, 31% had anemia and 15% had leucopenia [9]. In another study done by Yaramis A, a retrospective analysis of 314 pediatric patients of typhoid fever was done. The findings were suggestive of thrombocytopenia in 10% patients and anemia in 38% patients [10].

Positive blood culture is definitive evidence of enteric fever but it is positive in only 40-60% of cases [6]. Widespread and irrational prescription of antibiotics is cause of low sensitivity of blood culture. Thus, in the younger sibling, although the blood culture was negative but enteric fever cannot be ruled out as the presentation of younger sibling was very similar to the elder one (whose culture report was positive for *Salmonella typhi*). Enteric fever is known to be caused by poor sanitation and poor drinking water so both the siblings might have contracted it from same source. Stool and urine cultures become positive after first week of infection but their sensitivity is low, thus these are not routinely done. Bone marrow cultures are more sensitive but due to its invasive nature it is practically not used. Widal test is an easy, inexpensive and relatively non-invasive test but is not reliable because of high false positive results. This is due to presence of pre-existing antibodies from previous episodes of enteric fever or subclinical infection or presence of cross reacting antibodies due to some other non typhoidal infections. Thus definitive diagnosis of typhoid fever requires isolation of *Salmonella typhi* or *Paratyphi* from patient by blood culture but since patients often receive antibiotics prior to a laboratory diagnosis, very few cases have positive culture reports. Besides this, paucity of microbiologic facilities and long waiting time for culture results are reasons for the preference for Widal test. Thus, considering the low cost of Widal test and absence of other comparably cheap tests, is the test of choice in many developing countries like India [11].

The main treatment for enteric fever is an early antibiotic therapy, it reduces risk of mortality significantly. Treatment should not be delayed and there is no need to wait for culture report to start the treatment. Empiric treatment with ceftriaxone or a fluoroquinolone should be started [12]. Later, antibiotic can be changed according to sensitivity pattern. In the elder sibling, few multidrug resistant strains of salmonella were suspected due to failure of complete response by ceftriaxone so azithromycin was started in this patient and patient did show complete response with this drug. Azithromycin reduces clinical failure rate and duration of hospital stay in comparison to fluoroquinolones and relapse rate in comparison to ceftriaxone, when used in the treatment of multidrug resistant typhoid fever [13]. Thus, a high index of suspicion might help in early diagnosis and treatment of enteric fever and can help in preventing life threatening complications. In present case, early antibiotic therapy has proved to be of utmost importance in survival of patients.

CONCLUSION

Enteric fever is a common infection in children with varied presentation. Shock and haemorrhage are rare manifestations of enteric fever, so at times diagnosis of enteric fever in these cases is delayed. In

present case, we suspected dengue fever as first possibility but investigated child for enteric fever as well. Thus, a high index of suspicion for enteric fever in present case has helped salvage our patients. Therefore, patients presenting with manifestations like shock and haemorrhage should always be investigated for enteric fever as well. Multidrug resistant cases of enteric fever are on the verge so sensitivity pattern should always be done along with cultures and antibiotic should be given accordingly.

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