Rhabdomyolysis Complicating Typhoid Fever in a Child and Review of the Literature

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Abstract

Typhoid fever is an important cause of morbidity and mortality in the developing world, particularly in children, but is infrequently observed in the developed world and can occur in patients without a significant travel history. Rhabdomyolysis as a complication has rarely been reported, and never in a child. A child with *Salmonella enterica* serovar Typhi septicemia, complicated by rhabdomyolysis, encephalopathy and pancreatitis is described and all 15 reported cases to date are summarized.

Introduction

Typhoid fever is an important cause of morbidity and mortality in the developing world, particularly in children, but is infrequently observed in the developed world and can occur in patients without a significant travel history. Multiple organ systems are commonly affected. Rhabdomyolysis as a complication has rarely been reported, and never in a child. This report describes a child with *Salmonella enterica* serovar Typhi septicemia, complicated by rhabdomyolysis, encephalopathy and pancreatitis.

Case Report

A previously healthy 11-year old girl with no comorbidities presented with a 24-hour history of worsening limb pain, weakness and confusion. This was preceded by a 5-day history of fever, diarrhoea and vomiting but no abdominal pain. At initial assessment, she was febrile (101.5 °F) and tachycardic (HR 150), but normotensive (BP 90/65). She was encephalopathic and globally weak with normal deep tendon reflexes. Investigations revealed a normal haemoglobin and white cell count, but raised C-reactive protein (247 mg/l), urea (10 mmol/l), creatinine (150 mmol/l), hepatic enzymes (ALT 108 U/l, AST 481 U/l), lactate dehydrogenase (2399 iu/l), creatinine kinase (11,899 IU/L) and myoglobinuria. She subsequently developed severe epigastric pain with a transiently elevated lipase (10,769 U/l) and pancytopenia (nadir values: haemoglobin 95 g/L, white cell count 2.4 x10⁹/L and

platelets $72 \times 10^9/L$ (Table 1)). There was no evidence of bowel perforation on CT scan of the abdomen.

A diagnosis of rhabdomyolysis associated with acute kidney injury was made. She was admitted to intensive care for hydration with urinary alkalinization, and empiric antibiotic treatment with ceftriaxone, vancomycin and acyclovir.

Numerous investigations were conducted to determine a cause for the sepsis and rhabdomyolysis. Brain MRI demonstrated diffuse restricted diffusion extending to the deep white matter but CSF analysis was normal. Metabolic, autoimmune and toxicology testing were normal. *Salmonella enterica* serovar Typhi (*S. Typhi*) was isolated on blood cultures, with initial growth at 15 hours. The patient improved with supportive therapy and IV cefotaxime for 8 days. It was deemed that 7 days of appropriate IV antibiotics would likely be sufficient therapy, but the treating team were cautious because of the severity of the illness and continued antibiotics with IV azithromycin for 7 days and oral azithromycin for a further 7 days. Although the organism was fully sensitive (amoxicillin, cefotaxime, ciprofloxacin), therapy was changed to azithromycin given its excellent intra-cellular penetration and recognized efficacy against *S. Typhi*.^{1,2} She was discharged on day 17.

The patient had no history of recent travel to a typhoid endemic area. She was of Pacific Islander origin but had lived all of her life in New Zealand and Australia. No index case was identified. She made a complete recovery.

Discussion

Although the incidence of typhoid fever in Australia has steadily increased to around five per million person-year; this is comparatively low to other countries where it is endemic.³ In Australia, most cases occur in recently returned travellers from highly endemic areas but does occur sporadically.⁴

Rhabdomyolysis is the destruction of muscle fibres with release of cellular elements into the systemic circulation.⁵ A number of mechanisms have been proposed for rhabdomyolysis in typhoid fever, including sepsis-induced tissue hypoxia, direct bacterial invasion of myocytes, inhibition of muscle glycolytic enzymes and endotoxin-mediated damage.⁵⁻⁷ Myalgia is a common presenting complaint and may represent that muscle damage and rhabdomyolysis complicate typhoid fever more frequently than reported.⁸

Rhabdomyolysis has rarely been described in association with typhoid fever, and never in a child. In one literature review in 1996, *Salmonella* species was found to be the fourth most commonly cited cause of bacteria-induced rhabdomyolysis, with the majority due to non-typhoidal strains.⁹ However, the literature to date includes only 14 cases of *S. Typhi* infection associated with rhabdomyolysis (Table 2).¹⁰⁻²³ The mean age of cases is 28 years and there is a male preponderance. All cases had acute kidney injury and recovered normal renal function. The combination of encephalopathy, pancreatitis and rhabdomyolysis has only been reported twice previously and has not been associated with a particularly poor outcome.^{11,21} Encephalopathy was the most common neurological complication but diffuse axonal

polyneuropathy, cutaneous hyperesthesia and diplopia were also reported.^{11,17}

Pulmonary complications included bronchopneumonia and pleural effusion.^{11,17}

Myocarditis was only reported in one case.¹³ Reported hepatobiliary complications

include hepatitis, hepatosplenomegaly, ascites and conjugated

hyperbilirubinemia.^{13,16,17,18-22} However, it can be difficult to distinguish true hepatitis

from leakage of muscle cell transaminases.

Management of typhoid fever with rhabdomyolysis includes the administration of

antibiotic therapy as well as supportive care with hydration and urinary

alkalinization.⁵ Although complications can be severe, treatment is associated with

an excellent prognosis.

Conflicts of interest

None to declare

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Day of admission		1	2	4	7	8	9	11	14	17
White cell count x 10 ⁹ /L	(4.5 – 13.5)	5.9	2.3	2.4	5.8	7.1	8.8	7	8.1	
Hemoglobin (g/L)	(115 – 155)	127	109	95	104	101	95	91	100	
Platlets x10 ⁹ /L	(150 – 400)	101	86	72	126	161	225	368	416	
Urea (mmol/L)	(1.0 – 6.0)	10.8	12	14.2	8.5	7.3	6.5	4.5	7.9	9
Creatinine (umol/L)	(20 – 70)	150	207	212	74	62	54	64	77	90
Serum albumin (g/L)	(33 – 47)	34	25	21	23	25	27	31	41	42
AST (U/L)	(10 – 45)	481	451	399	321	262	199	121	74	48
ALT (U/L)	(5 – 45)	108	99	105	97	86	100	91	84	71
Creatinine Kinase (U/L)	(<50)	11899	11318	4108	1538	1342	1231	897	299	91
Lipase (U/L)	(<160)		416	1687	1605	9375	10769	3136	3280	2113
CRP (mg/L)	(<2.0)	247	238	120		17			6.5	

Table 1. Laboratory results.

Patient age in years, Sex	Year	Origin of report (Country S.Typhi acquired)	Symptoms prior to presentation (days)	Pancreatitis	Neurological	Cardiovascular	Hepatobiliary	Pulmonary	Recovery of Renal function	Renal Replacement Therapy	Reference
11, F	2016	Australia	5	Y	Y	N	N	N	Y	N	Reported case
21, F	2015	USA (India)	2	NR	N	N	NR	N	Y	N	Non ¹⁰
42, M	2011	UAE (India)	'Few days'	Y	Y	N	N	Y	Y	Y	Ali ¹¹
64, M	2010	India	7	NR	N	NR	N	N	Y	Y	Jhawar ¹²
34, M	2009	Qatar	3	NR	Y	Y	Y	N	Y	N	Al-aqueedi ¹³
23, M	2009	Qatar (Vietnam)	15	Y	N	NR	N	NR	Y	N	Khan ¹⁴
25, M	2004	USA (Pakistan)	5	NR	N	N	N	N	Y	N	Fisk ¹⁵
29, F	2004	UK (India)	14	NR	N	N	Y	N	Y	N	Simcock ¹⁶
16, F	2003	Lebanon	12	NR	Y	N	Y	Y	Y	Y	Dakdouki ¹⁷
21, M	2000	Canada (India)	9	N	Y	N	Y	N	Y	Y	Loutfy ¹⁸
20, F	1998	France	NR	NR	Y	N	Y	N	Y	N	Hazouard ¹⁹
18, M	1989	S. Africa	10	NR	N	N	N	N	Y	N	Mody ²⁰
17, F	1989	Senegal	5	Y	Y	N	N	N	Y	Y	Ginsburg ²¹
26, M	1986	USA	8	NR	Y	N	Y	Y	Y	N	Barnes ²²
32, M	1977	USA	6	NR	N	N	N	N	Y	N	Rheingold ²³

Table 2. Details of previously reported cases of typhoid fever complicated by rhabdomyolysis.