EDITORIAL

Rhabdomyolysis induced by *Salmonella enterica* serovar Typhi bacteraemia

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ABSTRACT

Rhabdomyolysis has been reported infrequently with salmonella infection. Since 1964, there have been at least 22 reports associated with gastroenteritis or bacteraemia. Twenty cases have been associated with non-typhoidal strains of *Salmonella*, with single reports of *Salmonella enterica* serovars Paratyphi and Typhi. A second case of typhoid fever associated with rhabdomyolysis was recently diagnosed in Ann Arbor, USA in a traveller returning from an endemic area. Prompt diagnosis and treatment resulted in a good outcome. Salmonella infection should be considered by clinicians as a possibility in the differential diagnosis of rhabdomyolysis.

Keywords Myoglobinuria, rhabdomyolysis, salmonellosis

Rhabdomyolysis is a clinical syndrome caused by damage of skeletal muscle with release of muscle enzymes (creatine kinase (CK), aminotransferases) and myoglobin haem pigment into the systemic circulation. Manifestations may vary from subclinical to severe, depending upon the extent and severity of muscle damage. Symptoms can range from mild myalgias to severe pain with weakness. Serum levels of CK are a hallmark of rhabdomyolysis, and myoglobin may be found in the urine. Acute renal failure, with associated metabolic acidosis and electrolyte abnormalities, occurs in part because of the direct toxic effects of haem and obstruction of renal tubules by pigment casts. Rhabdomyolysis has been associated with various non-infectious aetiologies, including extreme exertion, crush injuries and trauma, surgery, metabolic disorders, drugs and toxins [1–4], but has also been reported in association with a wide variety of infectious agents, most commonly viral or bacterial.

In a review of 59 virus-related cases, 25 were associated with influenza virus infection [2]. Among 60 bacteria-related cases in the English-language literature, *Legionella* spp., *Francisella*

spp., *Streptococcus pneumoniae*, *Salmonella* spp. and *Staphylococcus aureus* were reported most often, and mortality from all bacterial causes approached 40% [2]. There appears to have been an increase in the incidence of reported bacteria-related infections, with one case reported between 1966–77, 14 cases between 1976–83, and 45 cases between 1983–96 [2]. However, this apparent increase might be caused by better reporting, better microbiological recovery of organisms, or greater numbers of immunosuppressed patients.

Although common worldwide, *Salmonella enterica* serovar Typhi infections are seen only infrequently in USA medical centres. Salmonella infection is an infrequently reported cause of rhabdomyolysis [5–21], but since 1964 there have been at least 20 cases associated with bacteraemia or gastroenteritis caused by non-typhoidal salmonellae [6–18,20,21], and single reports associated with *Salmonella enterica* bacteraemia caused by serovars Paratyphi [19] and Typhi [5].

The single case of typhoid fever described above occurred in 1977, was blood culture-proven, and was acquired domestically (Table 1) [5]. Since that time, no cases of rhabdomyolysis associated with serovar Typhi infection have been reported. In 2000, Khan *et al.* [22] reported that two of 59 patients in a series of typhoid cases had 'myositis', with elevated CK levels, but neither of these cases had myoglobinuria.

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Case	Year reported	Peak serum CK level (IU/L)	Urine findings	Therapy	Complications; outcome
Case 1[a] [22]	1975	350/500	Unknown	RAD or AMP	Recovered
Cases 2–5[a] [22]	1975	> 500	Unknown	RAD or AMP	Recovered
Case 6[b] [5]	1977	17 160	Orthotolidine (+) RBCs (+)	AMP	Renal failure and hepatitis; partial recovery
Case in present report[b]	2002	42 165	Myoglobin (+)	CRO	Renal failure; recovered

Table 1. Characteristics of patients with probable or definite rhabdomyolysis associated with *Salmonella enterica* serovar Typhi bacteraemia

CK, creatine kinase; RBCs, red blood cells; AMP, ampicillin; CRO, ceftriaxone; RAD, chloramphenicol.
[a]probable; [b]definite.

Rhabdomyolysis or myositis induced by *S. enterica* serovar Typhi may be under-reported, as laboratory evaluation is pursued infrequently. In 1973, an outbreak of 105 cases of typhoid fever with bacteraemia occurred at a Florida camp for migrant labourers [23] (Table 1). CK levels were measured in 13 (12%) of the 105 patients, and were found to be elevated in four (31%) of the 13 patients investigated. Patients were treated with chloramphenicol or ampicillin, and there was no fatal outcome. Complications of gastrointestinal bleeding and neurological manifestations (delirium, meningitis), although rare, were each seen in five cases.

Proposed mechanisms for *Salmonella*-induced rhabdomyolysis include tissue hypoxia caused by sepsis, toxin release, direct bacterial invasion of muscle, and altered muscle metabolic capacity [2–4,20,24]. Animal studies of acute salmonella infection suggest a mechanism for altered muscle metabolism that leads to rhabdomyolysis. Using a rat model, Friman *et al.* [24] found dramatic suppression of oxidative and glycolytic enzyme capacity in rat skeletal muscle, as well as simultaneous upregulation of lysosomal enzyme activity. In the presence of acute salmonella infection, oxidative enzyme function was reduced to 65–83% of that seen in control animals, while glycolytic enzyme function was only 30–75% that of controls. It was concluded that ''*Salmonella* causes … a decline in the capacity … of muscle … to perform short time high intensity exercise as well as long time endurance efforts''.

A second case of typhoid fever associated with rhabdomyolysis was diagnosed recently in Ann Arbor, USA in a 25-year-old male, previously well, who had returned home just 7 days before admission after a 2-year stay in Pakistan. Five days before admission, subjective fevers, chills and an occipital headache developed. Diarrhoea was absent. Three days before admission, the patient reported that his urine had turned 'dark'.

He sought medical help 2 days before admission, at which time co-trimoxazole and quinine were prescribed empirically. After the development of abdominal pain and severe muscle spasms in the neck and legs, the patient presented to the University of Michigan Hospital Emergency Department for evaluation.

In Pakistan, the patient had travelled to rural areas, eaten local food, drunk tap water, and visited a friend who was ill with jaundice. He recalled mosquito bites, but denied sexual contacts, intravenous drug use, or vaccination against *S. enterica* serovar Typhi. He had a remote history of self-limited illness, characterised by fever and jaundice, in childhood. On examination, he had fever (39.4 °C), tachycardia (144 pulse beats/min), and diffuse abdominal tenderness without hepatosplenomegaly. Rash was absent. Leukocytosis (white blood cell count of 11.8×10^9/L with 73% polymorphonuclear cells), mild hepatitis with an aspartate transaminase level of 78 IU/L and an alanine transaminase level of 69 IU/L, acute renal failure with a serum creatinine level of 159 μmol/L, lactic acidosis (7.2 mmol/L), and rhabdomyolysis suggested by positive urine myoglobin (> 10 000 ng/mL) with an elevated serum CK level of 31 410 IU/L, were all noted. Coagulation studies were normal, with a platelet count of 26.0×10^9/L with an international normalised ratio of 1.1.

The patient was admitted to the intensive care unit for monitoring of multi-organ system dysfunction syndrome, hydration, urine alkalinisation, and antibiotic therapy with intravenous ceftriaxone 2 g four times every 24 h. The results of investigations for malaria, leptospirosis, brucellosis and trichinellosis were negative. Blood cultures drawn on admission grew a strain of *S. enterica* serovar Typhi that was sensitive to ceftriaxone, ciprofloxacin and co-trimoxazole.

With therapy, CK levels peaked at 42 165 IU/L, creatinine normalised, and lactic acidosis

resolved. Fever and abdominal pain abated over the next 5 days. The patient was discharged after hospitalisation for 7 days, with a prescription for 14 days of oral ciprofloxacin.

Given the high frequency of foreign travel and an increasing frequency of immigration, *S. enterica* serovar Typhi infection should be considered in the differential diagnosis of rhabdomyolysis, a rare and deadly complication of this infection. As described above, prompt diagnosis and treatment should result in a good outcome.

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