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

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Running Head Title

Rhabdomyolysis Complicating Typhoid Fever

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None to declare
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 x10⁹/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.¹² 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. In Australia, most cases occur in recently returned travellers from highly endemic areas but does occur sporadically.

Rhabdomyolysis is the destruction of muscle fibres with release of cellular elements into the systemic circulation. 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. Myalgia is a common presenting complaint and may represent that muscle damage and rhabdomyolysis complicate typhoid fever more frequently than reported.

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. However, the literature to date includes only 14 cases of S. Typhi infection associated with rhabdomyolysis (Table 2). 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. Encephalopathy was the most common neurological complication but diffuse axonal
polyneuropathy, cutaneous hyperesthesia and diplopia were also reported.\textsuperscript{11,17} Pulmonary complications included bronchopneumonia and pleural effusion.\textsuperscript{11,17} Myocarditis was only reported in one case.\textsuperscript{13} Reported hepatobiliary complications include hepatitis, hepatosplenomegaly, ascites and conjugated hyperbilirubinemia.\textsuperscript{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.\textsuperscript{5} Although complications can be severe, treatment is associated with an excellent prognosis.

\section*{Conflicts of interest}
None to declare

\section*{References}


Table 1. Laboratory results.

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<th>Day of admission</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>11</th>
<th>14</th>
<th>17</th>
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<tr>
<td>White cell count x 10⁹/L</td>
<td>(4.5 – 13.5)</td>
<td>5.9</td>
<td>2.3</td>
<td>2.4</td>
<td>5.8</td>
<td>7.1</td>
<td>8.8</td>
<td>7</td>
<td>8.1</td>
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<tr>
<td>Hemoglobin (g/L)</td>
<td>(115 – 155)</td>
<td>127</td>
<td>109</td>
<td>95</td>
<td>104</td>
<td>101</td>
<td>95</td>
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<tr>
<td>Platlets x10⁹/L</td>
<td>(150 – 400)</td>
<td>101</td>
<td>86</td>
<td>72</td>
<td>126</td>
<td>161</td>
<td>225</td>
<td>368</td>
<td>416</td>
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<tr>
<td>Urea (mmol/L)</td>
<td>(1.0 – 6.0)</td>
<td>10.8</td>
<td>12</td>
<td>14.2</td>
<td>8.5</td>
<td>7.3</td>
<td>6.5</td>
<td>4.5</td>
<td>7.9</td>
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<tr>
<td>Creatinine (umol/L)</td>
<td>(20 – 70)</td>
<td>150</td>
<td>207</td>
<td>212</td>
<td>74</td>
<td>62</td>
<td>54</td>
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<td>Serum albumin (g/L)</td>
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<td>21</td>
<td>23</td>
<td>25</td>
<td>27</td>
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<td>AST (U/L)</td>
<td>(10 – 45)</td>
<td>481</td>
<td>451</td>
<td>399</td>
<td>321</td>
<td>262</td>
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<td>105</td>
<td>97</td>
<td>86</td>
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<td>Creatinine Kinase (U/L)</td>
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<td>11899</td>
<td>11318</td>
<td>4108</td>
<td>1538</td>
<td>1342</td>
<td>1231</td>
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<td>Lipase (U/L)</td>
<td>(&lt;160)</td>
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<td>1687</td>
<td>1605</td>
<td>9375</td>
<td>10769</td>
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<tr>
<td>CRP (mg/L)</td>
<td>(&lt;2.0)</td>
<td>247</td>
<td>238</td>
<td>120</td>
<td>17</td>
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Table 2. Details of previously reported cases of typhoid fever complicated by rhabdomyolysis.

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<th>Patient age in years, Sex</th>
<th>Year</th>
<th>Origin of report (Country S.Typhi acquired)</th>
<th>Symptoms prior to presentation (days)</th>
<th>Pancreatitis</th>
<th>Neurological</th>
<th>Cardiovascular</th>
<th>Hepatobiliary</th>
<th>Pulmonary</th>
<th>Recovery of Renal function</th>
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<td>N</td>
<td>Y</td>
<td>N</td>
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<td>N</td>
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<td>N</td>
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