

# Myositis associated with *Salmonella paratyphi* A bacteremia appears to be common

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## ABSTRACT

**Background:** Fever and severe myalgia in a tropical country like India bring to mind leptospirosis, rickettsioses, dengue, and other viral fevers. Enteric fever is widely prevalent in Asia, but myositis has not been previously described in *Salmonella paratyphi* A bacteremia. **Materials and Methods:** Retrospectively, we recruited patients with enteric fever admitted to our treating unit over a 6-month period. Demography, historical, clinical, and laboratory data were obtained. Data of culture-positive *S. paratyphi* A patients were analyzed and were compared with those patients with culture-negative enteric fever. **Results:** Forty-three cases were found in total with 19 of *S. paratyphi* A bacteremia. Elevations in creatine kinase (CK) ranged from one-and-half to six times normal. Forty-seven percent had thrombocytopenia and alanine transaminase elevations, while aspartate transaminase elevations were seen in 17 patients, which corresponded to those with elevated CK levels. **Conclusions:** Myositis associated with *S. typhi* and *S. paratyphi* is very rare and is more often due to non-typhoidal Salmonellae. Elevated creatine kinase was seen in most of our patients with *S. paratyphi* A bacteremia. Such myositis has not been described previously and hence, myalgia with fever in a tropical country could be a harbinger of paratyphoid fever.

**Keywords:** Enteric fever, myositis, neurological complications, paratyphoid fever, typhoid fever

## Introduction

The typhoidal Salmonellae are *Salmonella enterica* serovar Typhi (*S. typhi*) and *Salmonella enterica* serovar Paratyphi A (*S. paratyphi* A), B, and C.<sup>[1]</sup> These typhoidal Salmonellae belong to the *S. enterica* subspecies I of *S. enterica* that also includes *S. Typhimurium* causing gastroenteritis and *S. Choleraesuis* that causes invasive bacteremia.<sup>[2]</sup> *S. paratyphi* infections have begun replacing *S. typhi* as the predominant cause of enteric fever.<sup>[1]</sup> Indian studies have shown surges in *S. paratyphi* isolates from patients with enteric fever.<sup>[1]</sup> The five manifestations of Salmonella infections are enteric fever, chronic carriage, gastroenteritis, bacteremia, and focal infections. The latter three arise due to non-typhoidal Salmonellae like *S. typhimurium*. Salmonella-related

muscle involvement is usually in the form of rhabdomyolysis, polymyositis, and pyomyositis. The most common organism causing focal muscle infections is *S. enteritidis*.<sup>[3]</sup> Typhoid-related myositis was rare even in Osler's series of 829 (1/829).<sup>[4]</sup> *S. typhi* has been reported to cause rhabdomyolysis (>20 cases) and focal abscesses.<sup>[5]</sup> *S. paratyphi* is the most common serovar of the paratyphoid group.<sup>[6]</sup> *S. paratyphi* A has never previously been reported to cause myositis or acute kidney injury. We report 18 patients of *S. paratyphi* bacteremia-associated myositis who had been treated in our medical unit over a period of 6 months.

## Materials and Methods

After obtaining approval from the Institute Ethics Committee (IEC/PP/2016/44), data were retrospectively collected from consecutive patients admitted to the Department of Medicine, Indira Gandhi Medical College & Research

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Institute, between 01 February 2016 and 31 July 2016. All patients  $\geq 13$  years with a discharge diagnosis of either “Enteric fever,” “Typhoid fever,” or “Paratyphoid fever” were recruited. Demographic data, medical history, and clinical findings were noted. Laboratory data such as liver function tests (LFT), creatine kinase (CK), Widal, and blood culture reports were obtained. Patients with *S. paratyphi A* bacteremia were considered as cases. Those with symptoms and four-fold elevations in Widal (*S. typhi* or *S. paratyphi*), or a single admission titer of 1:320 were taken as culture-negative enteric fever. A symptom-complex of myalgia with or without objective weakness and elevated CK obtained at admission was considered as myositis. History of dark urine, muscle tenderness, and swelling, serum potassium and serum creatinine were focused upon to rule out rhabdomyolysis. Urine myoglobin and Lactate dehydrogenase (LDH) were not performed because of their non-availability. None of the patients underwent a muscle biopsy.

Data were entered in an Excel sheet and analyzed using IBM SPSS22. Numerical data were analyzed by descriptive statistics. For continuous variables, independent samples T test was used to compare patients with and without *S. paratyphi A* bacteremia. Pearson correlation analysis was performed for the duration of symptoms, hospital stay, alcohol and tobacco use, LFT, renal function tests, CK, and hematological parameters. Statistical significance was defined as a *P* value  $< 0.05$ .

## Results

There were 19 patients with culture-positive *S. paratyphi A*, 18 being men. CK levels were missing in the lone female patient [Table 1]. Two instances of co-infection—one with scrub typhus and another with leptospirosis were found. Fifty percent presented with fever  $\leq 1$  week duration and 16 patients stayed  $> 1$  week in the hospital (mainly to complete a 7-day ceftriaxone course). Fourteen (14/42) had used alcohol and 7/42 smoked. CK elevations ranged between  $1\frac{1}{2}$  and 6 times normal ( $< 170$ ). Thrombocytopenia and alanine aminotransferase (ALT) elevations were seen in 47%. Complications such as acute kidney injury (AKI), cerebral edema, oral ulcers, earache (2/45, in the non-bacteremic group), pleurisy, dizziness (postural hypotension), and myocarditis/shock/upper gastrointestinal bleed (in the patient with leptospirosis+ typhoid fever) were observed. LDH (in patient no. 4) and urine myoglobin were not performed routinely because of its unavailability in our institution. All were negative for HIV.

Thrombocytopenia, CK, CK-AST ratio, and longer hospital stay were significant in the bacteremic group [Table 2]. Duration of symptoms positively correlated with alcohol quantity ( $r = 710$ ;  $P < 0.001$ ) and with elevations in alkaline phosphatase ( $r = 0.636$ ;  $P < 0.001$ ). Aspartate aminotransferase (AST) correlated positively with total leukocyte count ( $r = 0.321$ ;  $P = 0.043$ ), while alanine aminotransferase (ALT) negatively correlated with both De Ritis ratio and CK-AST ratio ( $r = 516$ ;  $P = 0.001$  and  $r = 326$ ;  $P = 0.37$ ). The De Ritis ratio had a significant positive

correlation with both the CK-AST ratio ( $r = 0.436$ ;  $P = 0.004$ ) and creatinine ( $r = 0.325$ ;  $P = 0.02$ ). Patient no. 18 had cerebral edema necessitating mannitol for 48 hours. All 19 patients received 7 days of ceftriaxone and needed 4–5 days for defervescence. Because all our isolates were sensitive to both ampicillin and cotrimoxazole, patients were additionally, given a 7-day course of the latter. Patients who had been initiated on azithromycin at admission for prominent respiratory symptoms or signs were not given cotrimoxazole. One patient with diabetes mellitus, received ceftriaxone for 14 days because defervescence occurred only on the 12<sup>th</sup> day. We could not localize any focal abscesses in him. All patients received advice regarding eating street food, hygienic practices, and safe sanitation.

## Discussion

Enteric fever is the most significant clinical manifestation of *S. enterica*.<sup>[2]</sup> *S. paratyphi* contributes to  $> 5$  million cases/year, globally.<sup>[7]</sup> In 2005, the incidence of *S. paratyphi* to *S. typhi* compared among study populations in India, China, Indonesia, and Pakistan indicated that *S. paratyphi* contributed to a significant percentage of cases.<sup>[8]</sup> The incidence in South Asia is 40–80 cases/100,000 person-years and is increasing where the disease burden is high.<sup>[9]</sup> In 1975, *S. paratyphi* was reported to be the third most common, while *S. typhi* constituted 57% of the 47 human serotypes at that time.<sup>[10]</sup> The prevalence of paratyphoid fever is most commonly reported with *S. paratyphi A*. The prevalence of *S. paratyphi A* has been less than 8% in most study sites.<sup>[11]</sup> There is a seasonal trend in incidence of enteric fever in Asia, peaking between May and October that are the most warm months of the year that may lead to higher growth of bacteria on food and corresponds to people searching for food or drinks as refreshments during these months. Hot weather and water scarcity may also lead to ingesting of contaminated water and drinks.<sup>[12]</sup> In a retrospective study from Nepal, blood culture data over 23 years revealed that *S. paratyphi A* constituted 30% of all isolates of the *S. enterica* subspecies I.<sup>[13]</sup> The Indian burden of paratyphoid fever is  $> 100/100,000$  person-years.<sup>[14]</sup> Southern and Western India have a greater burden than that of Northern and Eastern India.<sup>[15]</sup> *S. paratyphi* has been isolated from 50% of returning travelers (with enteric fever) from the Indian subcontinent.<sup>[16]</sup> In our own institution (2011–2014), *S. paratyphi* constituted 50.8% of *Salmonella* isolates; in 2014, *S. paratyphi* contributed to a staggering 91.3% of isolates.<sup>[17]</sup> In a study from Chennai over a 2-year period, 134/322 *Salmonella* isolates were of *S. paratyphi A*.<sup>[18]</sup> In Karnataka,  $\geq 50\%$  isolates were because of *S. paratyphi* and a seasonal increase (monsoon) was also observed.<sup>[9]</sup> In hospital-based studies, 10–54.5% of enteric fever cases are attributable to paratyphoid fever.<sup>[15]</sup>

Clinical features of paratyphoid infection are often indistinguishable from typhoid fever.<sup>[16]</sup> Myalgia is seen in 20% and arthralgia in  $< 5\%$  of patients with enteric fever.<sup>[7]</sup> Myalgia was universal in our setting; additionally, mild encephalopathic changes such as confusion or apathy were also observed. Musculoskeletal problems such as osteomyelitis, myositis,

**Table 1: Demography, clinical features, and investigations of patients with *Salmonella paratyphi A* bacteremia**

Age/sex/occupation	Illness duration (days)	Hospital stay (days)	Other diagnoses/complications	Widal O/H/AH/BH	Creatine kinase (U/L<170)	AST (U/L)	ALT (U/L)	TLC (×10 <sup>9</sup> /L)	Platelet (×10 <sup>9</sup> /L)
15/male/student	20	8		<1:80/80/80/80	215	55.0	27.0	6.1	227
16/male/student	7	11		1:80/80/160/80	320	67.0	35.0	7.6	123
16/male/student	15	8		<1:80/80/80/80	326	34.0	18.0	5.4	202
19/male/laborer	10	11		<1:80/80/80/80	679	46.0	34.0	4.4	182
21/male/painter	15	7		<1:80/80/80/80	381	102.0	84.0	6.8	130
23/male/engineer	3	10	Oral ulcers	NA	225	60.0	32.0	2.8	120
24/male/student	6	9		<1:80/80/80/80	836	56.0	33.0	6.0	193
25/male/unemployed	7	21	Diabetes mellitus; oral ulcers	<1:80/80/80/80	730	227.0	248.0	8.5	247
27/male/mechanic	25	9		1:80/80/320/80	80	41.0	45.0	6.8	145
30/male/policeman	3	10	ADS; alcoholic hepatitis	<1:80/80/80/80	230	88.0	217.0	10.9	110
30/male/mechanic	10	9		1:160/80/80/80	1047	27.0	10.0	6.5	192
31/male/NA	18	20		1:80/80/160/80	189	53.0	48.0	8.6	152
35/male/mason	6	12	HCV positivity; oral ulcers	<1:80/80/80/80	260	41.0	45.0	9.2	203
36/male/NA	3	9	ADS; AWS	1:80/80/160/80	237	97.0	63.0	6.0	39
37/male/driver	45	9		1:<80/<80/160/<80	228	71.0	64.0	6.3	181
38/male/NA	7	7		<1:80/80/80/80	266	85.0	78.0	6.3	135
40/female/NA	5	8		<1:80/80/80/80	-	67.0	53.0	4.7	163
46/male/auto driver	19	10	Dyslipidemia; AKI; cerebral edema	1:80/80/160/80	365	53.0	40.0	5.4	131
70/male/cashier	7	4	Hypertension; AKI	<1:80/80/80/80	180	52.0	29.0	5.9	106

AST: Aspartate transaminase; ALT: Alanine transaminase; TLC: Total leukocyte counts; NA: Not available; ADS: Alcohol dependent syndrome; HCV: Hepatitis C virus; AWS: Alcohol withdrawal syndrome; AKI: Acute kidney injury

**Table 2: Comparison of clinical and laboratory data between the two groups**

Variables	Culture positive <i>Salmonella paratyphi A</i>	Culture negative enteric fever	P
Age (years)	32.7±14.0	27.4±5.7	0.48
Hospital stay (days)	10.1±4.0	6.8±1.9	0.004
Duration symptoms (days)	12.0±10.2	14.1±8.2	0.48
Time to defervesce (days)	4.6±2.5	4.4±0.9	0.35
Alcohol (years)	3.68±5.0	1.57±5.2	0.19
Pulse (beats/min)	94.0±14.5	91.6±10.1	0.38
SBP (mmHg)	110.5±13.1	115.8±10.2	0.20
Respiratory rate per min	20.4±4.5	20.2±9.1	0.95
Creatinine (mg/dL)	0.9±0.2	1.0±0.2	0.59
AST (U/L ≤35)	69.5±43.2	101.7±82.8	0.11
ALT ((U/L ≤40)	63.3±43.3	101.7±82.8	0.86
ALP (U/L ≤100)	98.8±45.3	134.1±130.3	0.24
TLC (×10 <sup>9</sup> /L)	6.53±1.8	6.9±2.3	0.49
Neutrophils (×10 <sup>9</sup> /L)	64.9±11.8	66.7±9.34	0.58
Platelets (×10 <sup>9</sup> /L)	156.8±49.5	204.1±84.4	0.03
Creatinine kinase (U/L)	377.1±263.7	310.07±282.4	0.49

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; TLC: Total leukocyte counts; SBP: Systolic blood pressure

and abscesses have been described only as case reports.<sup>[19]</sup> Myositis is muscle inflammation due to both infectious and non-infectious (metabolic, inflammatory, and genetic) causes.<sup>[20]</sup> Infectious myositis is classified into non-pyogenic generalized (the focus of our study) and pyogenic focal types.<sup>[20]</sup> Infection-related

myositis occurs due to viral (influenza), bacterial (tropical myositis), mycobacterial (tuberculosis), fungal (candidiasis), and parasitic (toxoplasmosis) diseases. Bacteria and fungi are more likely to cause focal myositis.<sup>[21]</sup> Myositis due to *Salmonella* species is rare and has been reported with *S. typhi* and *S. enteritidis*.<sup>[22]</sup> Myalgia, with or without myositis, is observed in rickettsial fevers (scrub typhus), leptospirosis, dengue, HIV infection, Lyme disease, and infective endocarditis; the first three are common in a tropical setting like ours. We had one case of scrub typhus and leptospirosis each co-existing with enteric fever. More >50% *Salmonella*-related pyomyositis are due to *S. enteritidis* species.<sup>[23]</sup> Collazos *et al.*, had compiled 31 cases of *Salmonella*-related focal muscle infections reported between 1962 and 1999. Diabetes mellitus, HIV infection, alcoholism, cancer chemotherapy, steroid use, and trauma are common predisposing factors for pyomyositis.<sup>[3,24]</sup> *S. typhi*-related pyomyositis has been described in an immunocompetent male from India.<sup>[24]</sup> Naidoo *et al.*, described four people with typhoid polymyositis, with three from the same family and suggested a genetic predisposition.<sup>[25]</sup> Other focal extraintestinal abscesses arising due to *S. paratyphi* infections such as the breast and kidneys have also been reported, all of them being in young adults.<sup>[19,26]</sup> Only one case of *S. paratyphi B*-related myositis and rhabdomyolysis has been reported, but this patient also had hepatitis and disseminated intravascular coagulation.<sup>[27]</sup> Mechanisms of myositis/rhabdomyolysis include bacterial invasion of the muscle, sepsis-related tissue hypoxia, and altered metabolic capacity of the muscle.<sup>[28]</sup>

Under-reporting of myositis probably occurs because CK is not a routinely performed test in febrile patients unless weakness, calf pain, or cola-colored urine is present, or when leptospirosis is part of the differential diagnosis. Mirsadraee *et al.*, reported that AST correlated more with CK levels rather than liver disease, thereby proposing that the transaminase elevations in typhoid fever may be due to muscular origin.<sup>[29]</sup> In our series, CK correlated significantly with both the De Ritis ratio ( $r = 0.786$ ;  $P < 0.001$ ) and CK-AST ratio ( $r = 0.436$ ;  $P = 0.04$ ). Most of our patients had both CK and ALT elevations, while only 10 had increases in AST.

## Limitations

One reason attributed to the increasing incidence of *S. paratyphi* is the probable use of vaccines that predominantly protects against *S. typhi*.<sup>[1]</sup> No vaccination history was available even though cross-protection may exist for some vaccines such as Ty21avv.<sup>[30]</sup> Vaccines for *S. paratyphi* are currently not available.<sup>[6]</sup> We did not have the facility for LDH and urine myoglobin, so rhabdomyolysis could not be confirmed. The sample size was small, and data were from a single medical unit. We did not have access to data from the other four medical units and the Pediatrics department. A surveillance model similar to the Chinese National Infections Disease Surveillance System may improve data collections.<sup>[15]</sup>

## Conclusions

Fever and severe myalgia in a tropical country like India bring to mind leptospirosis, rickettsioses, dengue, and other viral fevers. Enteric fever is not usually considered in the differential diagnosis of myalgia with elevated CK in the tropics. *Salmonella* infections have been described in literature as a cause of focal myositis, while our patients appeared to have diffuse myositis associated with enteric fever. Although only one report of paratyphoid fever has been shown to cause myositis, because of our findings, it is possible that myositis in enteric fever may have been unrecognized, and therefore, under-reported. Thus, physicians need to be aware of enteric fever-associated myositis that appears to be common in bacteremic patients. However, we are amid a paratyphoid epidemic, one should remember that myalgia could be a harbinger of *S. paratyphi* infection and myositis may be more frequently seen than not.

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## Conflicts of interest

There are no conflicts of interest.

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