Factors Associated with Encephalopathy in Patients with *Salmonella enterica* Serotype Typhi Bacteremia Presenting to a Diarrheal Hospital in Dhaka, Bangladesh

Daniel T. Leung,* Jori Bogetz,† Megumi Itoh,‡ Lakshmi Ganapathi, Mark A. C. Pietroni, Edward T. Ryan,§ and Mohammad Jobayer Chisti‡

Division of Infectious Disease, Massachusetts General Hospital, Boston, Massachusetts; Department of Medicine, Harvard Medical School, Boston, Massachusetts; Department of Pediatrics, Stanford University School of Medicine, Palo Alto, California; Department of Pediatrics, Children’s Hospital Boston, Boston, Massachusetts; Dhaka Hospital and Centre for Nutrition and Food Security, International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh; Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts

Abstract. To characterize clinical correlates of typhoid fever-associated encephalopathy, we performed a retrospective chart review of patients with *Salmonella enterica* serotype Typhi bacteremia who were hospitalized at the International Centre for Diarrhoeal Disease Research, Bangladesh, from February of 2009 to June of 2011. Of 207 patients bacteremic with *Salmonella* Typhi who were ≥5 years of age, we identified 43 (21%) patients with encephalopathy. Univariate analysis revealed that patients with encephalopathy more often presented at ages of 10–24 years and had severe dehydration, low oxygen saturation, high respiratory rate, low leukocyte count, low platelet count, and Widal flagellar H agglutinin (TH) titer ≥1:640 compared with typhoid patients without encephalopathy. Multivariate analysis using logistic regression showed that age, dehydration, leukocyte count, and Widal TH titer were independently associated with encephalopathy. Our findings suggest that age, severity of disease, and immune responses are associated with encephalopathy during *Salmonella* Typhi bacteremia, perhaps reflecting the impact of prominent inflammatory responses.

INTRODUCTION

Typhoid fever is a systemic illness caused by infection with *Salmonella enterica* serotype Typhi. It affects over 21 million people each year worldwide, with the highest incidence among infants and children living in southcentral and southeast Asia.1 Initial signs and symptoms include fever, chills, anorexia, malaise, headache, abdominal pain, and constipation. Although the most-studied complications of severe typhoid fever include intestinal perforation and hemorrhage,2,3 numerous extraintestinal manifestations, including encephalopathy, can occur, especially in severe disease.4 The term typhoid originates from the Greek word typhos meaning smoke, which refers to the apathy and confusion associated with the disease.5 The work by Osler6 described the “typhoid state” as a semiconscious state characterized by a blank stare, “muttering” incoherent speech, and an arousable but not interactive patient.6 Case series from the United States,7 Nigeria,8 India,9 and Bangladesh10 show that up to 75% of patients hospitalized with typhoid fever may have neuropsychiatric manifestations, mostly characterized as stupor, “delirium,” or a “confusional state,” although myelitis, cerebellitis, parkinsonism, insomnia, and acute psychosis have also been described.7-10 Historically, typhoid encephalopathy has been associated with mortality rates of up to 50% even with antibiotics, although recent surveys are lacking.11,12 The pathophysiology of the various neuropsychiatric manifestations of typhoid fever, including encephalopathy, remains to be elucidated.

Although antibiotics remain the mainstay of treatment of typhoid fever, several small studies suggest that concurrent high-dose dexamethasone therapy may have substantial benefits in reducing mortality and morbidity of patients with typhoid encephalopathy.11,13,14 Moreover, studies also suggest that delaying steroid administration may result in increased mortality13 or a higher rate of relapse.15 Thus, prompt recognition of typhoid encephalopathy before availability of culture data is important for initiation of appropriate therapy. Few studies have recently examined the clinical and demographic characteristics associated with encephalopathy in typhoid fever. Thus, we conducted a retrospective analysis of patients presenting to our hospital with bacteremia-confirmed typhoid fever to identify factors associated with encephalopathy.

MATERIALS AND METHODS

Study site. We conducted a retrospective chart review at the Dhaka Hospital of the International Center for Diarrhoeal Disease and Research, Bangladesh (icddr,b). We obtained case records from the electronic charting system to identify all patients admitted between February 15, 2009 (the initiation date of the electronic system) and June 30, 2011 who had blood cultures positive for *S. enterica* serotype Typhi. As a negative comparator group, we also identified patients bacteremic with *Salmonella* enterica serotype Typhi who were hospitalized at the International Centre for Diarrhoeal Disease Research, Bangladesh, from February of 2009 to June of 2011. Of 207 patients bacteremic with *Salmonella* Typhi who were ≥5 years of age, we identified 43 (21%) patients with encephalopathy. Univariate analysis revealed that patients with encephalopathy more often presented at ages of 10–24 years and had severe dehydration, low oxygen saturation, high respiratory rate, low leukocyte count, low platelet count, and Widal flagellar H agglutinin (TH) titer ≥1:640 compared with typhoid patients without encephalopathy. Multivariate analysis using logistic regression showed that age, dehydration, leukocyte count, and Widal TH titer were independently associated with encephalopathy. Our findings suggest that age, severity of disease, and immune responses are associated with encephalopathy during *Salmonella* Typhi bacteremia, perhaps reflecting the impact of prominent inflammatory responses.

Case definition. Patients with encephalopathy were identified based on similar criteria as the criteria of previous studies7,8 as patients with one or more of the following mentioned in their chart: (1) confusion, disorientation, slurred speech, or altered mental status or (2) Glasgow Coma Scale (GCS) < 15 without alternative diagnosis.16 We excluded from our study all patients < 5 years of age because of the non-standardized mental status assessment of young children available in the charting system.

Data abstraction. We collected admission demographic, clinical, and laboratory data from the electronic charting system. The term typhoid originates from the Greek word typhos meaning smoke, which refers to the apathy and confusion associated with the disease.5 These authors contributed equally. These authors are co-senior authors.
system. The following variables were identified in each chart: age, gender, comorbid conditions, pre-admission antibiotics, presenting symptoms, duration of symptoms before admission, and physical examination findings, including neurologic exam, height, weight, and level of dehydration. We also collected admission laboratory data, including peripheral blood cell counts, electrolytes, renal and liver function, Widal test, and culture data, including antimicrobial sensitivity of the isolate.

Ethical review. The study was approved by the Ethical Research Committee of the icddr,b and the Institutional Review Board of the Massachusetts General Hospital.

Data analysis. We compared the characteristics of bacteremic patients with evidence of encephalopathy and bacteremic patients without encephalopathy. For continuous variables, we used the Student t test (normally distributed data as assessed by the Shapiro–Wilk test) or the Mann–Whitney U test (for non-parametric data) to compare groups. For categorical variables, we used Fisher exact tests. We used logistic regression to determine multivariate predictors of encephalopathy. Gender plus variables with \( P < 0.01 \) from univariate analysis that had < 25% missing data were entered into multivariate logistic regression. We performed statistical analyses using SPSS 17.0 (SPSS Inc., Chicago, IL). Statistical significance was defined as a two-tailed \( P \) value < 0.05.

RESULTS

We identified a total of 323 patients who had blood cultures positive for Salmonella Typhi during the study period, including 207 patients \( \geq 5 \) years of age. Of these patients, we identified 43 patients (21%) who fulfilled our clinical criteria for encephalopathy at the time of admission (before availability of microbiologic analysis of blood). The age distribution of those patients with and without encephalopathy is depicted in Figure 1. Approximately 25–32% of those patients aged 10–24 years had features of encephalopathy compared with 5–12% of those patients in other age groups (\( P = 0.001 \)). We identified 52 patients \( \geq 5 \) years of age with non-Salmonella Gram-negative bacteremia during the same period. Only three (6%) patients were identified with encephalopathy per our definition, and no cases of encephalopathy occurred in individuals 10–24 years of age.

Univariate comparisons of historical, clinical, and laboratory data are shown in Table 1. In addition to age association, we found that patients with encephalopathy were significantly more likely to live in a slum or tin shed (\( P = 0.03 \)) and have severe dehydration on exam (\( P < 0.001 \)), a high respiratory rate on admission (\( P = 0.03 \)), a low oxygen saturation (\( P = 0.02 \)), a low white blood cell count (\( P = 0.001 \)), a low platelet count (\( P < 0.001 \)), and a Widal flagella H agglutinin (TH) \( \geq 1:160 \) (\( P < 0.001 \)). The magnitude or duration of fever, water source, gender, antibiotic resistance pattern of the subsequent isolate, use of pre-admission antibiotics, and Widal somatic O agglutinin titer were not associated with encephalopathy.

In multivariate logistic regression analysis (Table 2), we found that age of 10–24 years, severe dehydration, low white blood cell count, and Widal TH \( \geq 1:640 \) were statistically significant independent predictors of presence of encephalopathy. All patients received antibiotics and steroids at the discretion of the attending physician. Most patients received ceftriaxone, and dexamethasone was administered to 1 of

![Figure 1](image-url)
164 bacteremic patients without encephalopathy and 30 of 43 patients with encephalopathy. Of 207 total patients, there was only one death, which occurred in a patient with encepha-
lopathy. This patient was 18 years old, had a GCS of 4 on admission, and died within 24 hours of admission because of shock. All others recovered.

**DISCUSSION**

Typhoid fever is a major cause of mortality and morbidity in developing countries worldwide, with the highest geo-
graphic burden of disease in Asia, especially in major urban centers.17–19 Encephalopathy is a potentially fatal compi-
clation of typhoid fever, and here, we describe clinical and demographic factors associated with this disease entity in Dhaka, Bangladesh.

We show that older children and young adults have higher rates of encephalopathy among those patients hospitalized with *Salmonella* Typhi bacteremia than younger children and older adults. In multivariate analysis, age of 10–24 years was independently associated with encephalopathy. Studies have shown that differences in mean age of patients with typhoid vary by region, and they are likely related to burden of disease, with lower ages in countries with high incidence.20 In population-based surveillance from endemic areas, rates of *Salmonella* Typhi bacteremia are highest in those patients aged < 5 years.17,18,20,21 However, hospital-based surveillance studies have shown that older children and young adults account for the majority of hospitalizations for typhoid fever,10,19 and they suggest that younger adults have greater neuropsychiatric morbidity during typhoid fever compared with older adults.22 The reasons behind these findings are unclear. Because encephalopathy may be associated with severe typhoid and because Gram-negative bacteremia is uncommon in older children and young adults, it is possible that this finding may be a response of this age group to Gram-
negative bacteremia itself; however, we were unable to iden-
tify any cases of encephalopathy in adolescents and young adults with non-*Salmonella* Typhi Gram-negative bacteremia at the icddr,b during the same period using the same criteria. It is also possible that older children and young adults are able to mount more prominent inflammatory responses than younger children and that encephalopathy may be associated with such responses. This possibility is also supported by the observation that intestinal perforation during typhoid is also more common in older children and adults than young children and that perforation may be associated with hyperplasia of intesti-
nal lymphoidal tissue caused by previous antigenic expos-
ure.3,10 Although other investigators have also hypothesized that a greater inflammatory response is responsible for patho-
genesis of severe typhoid, including encephalopathy,11,21 the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 10–24 years</td>
<td>3.7</td>
<td>1.1–12</td>
<td>0.03</td>
</tr>
<tr>
<td>Female</td>
<td>0.7</td>
<td>0.3–1.8</td>
<td>0.49</td>
</tr>
<tr>
<td>Severe dehydration</td>
<td>4.5</td>
<td>1.8–11.2</td>
<td>0.001</td>
</tr>
<tr>
<td>WBC count</td>
<td>0.8</td>
<td>0.7–0.99</td>
<td>0.04</td>
</tr>
<tr>
<td>Widal TH titer ≥ 1:640</td>
<td>5.4</td>
<td>1.9–15.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio; WBC count = admission peripheral blood white blood cell count.
species by macrophages induced by *Salmonella Typhi* endotoxin.\(^{31}\) Unfortunately, there has been a lack of studies to confirm this suspicion. Small studies of encephalopathy associated with non-typhoidal *Salmonella* infection have shown that proinflammatory cytokines are elevated in both cerebrospinal fluid (CSF) and serum,\(^{29-31}\) and cytokine-induced neurotoxicity has been suggested as the cause. No studies to date have measured CSF cytokines in *Salmonella Typhi* infection. Studies from plasma of acute typhoid patients have shown elevations in proinflammatory cytokines interleukin (IL)-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-R, and IL-1RA in acute disease that decrease with therapy.\(^{32}\) Interestingly, a study of *ex vivo* lipopolysaccharide (LPS)-stimulated whole blood from patients with *Salmonella Typhi* infection showed that those patients with complicated disease had lower levels of the proinflammatory cytokines IL-1βL and TNF-α in the acute phase than those patients with uncomplicated disease.\(^{33}\) IFN-γ cellular responses are also elevated during early typhoid fever, with the majority of this response reflecting CD4 cells.\(^{34}\) As such, it is possible that encephalopathy may reflect a poorly understood effect of a prominent inflammatory response on the CNS.

There are several limitations to this study. First, this study is a retrospective chart review study extracting data from a clinical record. Second, complete data were not available for all patients. Third, we did not include children less than 5 years of age in our analysis. Fourth, we limited our analysis to patients with confirmed *Salmonella Typhi* bacteremia. Despite these limitations, however, our analysis suggests that typhoid encephalopathy may still be common in this urban area and that prospective evaluation and standardized characterization of encephalopathy during *Salmonella Typhi* bacteremia may be warranted.

In conclusion, we show that 21% of patients hospitalized at a diarrheal hospital in Bangladesh with *Salmonella Typhi* bacteremia showed features of encephalopathy and that most of these cases occur in individuals aged 10–24 years. We also show that age, a Widal TH ≥ 1:640, leucopenia, and severe dehydration are independently associated with encephalopathy, and we hypothesize that encephalopathy in typhoid fever may be associated with an overabundant inflammatory response.

**Received December 2, 2011. Accepted for publication January 26, 2012.**

**Acknowledgments:** This research study was funded by International Centre for Diarrhoeal Disease Research, Bangladesh and its donors, which provide unrestricted support to International Centre for Diarrhoeal Disease Research, Bangladesh for its operations and research. Current donors providing unrestricted support include the Australian Agency for International Development (AusAID), the Government of the People’s Republic of Bangladesh, the Canadian International Development Agency (CIDA), the Swedish International Development Cooperation Agency (Sida), and the Department for International Development, United Kingdom (DFID). This study was also supported by grants from the National Institutes of Health, including Fogarty International Center Grant D43 TW005572, American Recovery and Reinvestment Act Supplement (to D.T.L.), a Postdoctoral Research Fellowship in Global Infectious Diseases from the Harvard Global Health Institute (D.T.L.), a Postdoctoral Fellowship in Tropical Infectious Diseases from the American Society of Tropical Medicine and Hygiene/Burroughs Wellcome Fund (D.T.L.), and National Institute of Allergy and Infectious Diseases Grant U01 AI077883 (to E.T.R.).

**Authors’ addresses:** Daniel T. Leung and Edward T. Ryan, Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA, E-mails: dleung@partners.org and etryan@partners.org. Jori Bogetz and Megumi Itoh, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, E-mails: jbogetz@stanford.edu and mitoh@stanford.edu. Lakshmi Ganapathi, Department of Pediatrics, Children’s Hospital Boston, Boston, MA, E-mail: Lakshmi.Ganapathi@childrens.harvard.edu. Mark A. C. Pietroni and Mohammad Jibayer Chisti, Dhaka Hospital and Centre for Nutrition and Food Security, Intensive Care Unit and Respiratory Ward, International Centre for Diarrhoeal Disease Research, Bangladesh, Mohakhali, Dhaka, Bangladesh, E-mails: markp@icddrb.org and chisti@icddrb.org.

**REFERENCES**


