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

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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 extra-intestinal 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.² The work by Osler⁵ described the “typhoid state” as a semiconscious state characterized by a blank stare, “muttering” incoherent speech, and an arousable “typhoid state” as a semiconscious state characterized by a blank stare, “muttering” incoherent speech, and an arousable

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.²⁻⁷ 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.¹¹⁻¹³¹⁴ 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 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 *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumanii* complex, which are the three most common non-*Salmonella* causes of Gram-negative bacteremia among patients aged 5 years and older at our institution.

Case definition. Patients with encephalopathy were identified based on similar criteria as the criteria of previous studies¹¹⁻¹² 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 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) $\geq 1:640$ ($P < 0.001$). 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.** Patients bacteremic with *S. enterica* serotype Typhi by age group and presence of encephalopathy.
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 encephalopathy. 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 geographic burden of disease in Asia, especially in major urban centers. Encephalopathy is a potentially fatal complication 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. In population-based surveillance from endemic areas, rates of *Salmonella* Typhi bacteremia are highest in those patients aged < 5 years. However, hospital-based surveillance studies have shown that older children and young adults account for the majority of hospitalizations for typhoid fever, and they suggest that younger adults have greater neuropsychiatric morbidity during typhoid fever compared with older adults. 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 identify 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 prominent in older children and adults than young children and that perforation may be associated with hyperplasia of intestinal lymphoidal tissue caused by previous antigenic exposure. Although other investigators have also hypothesized that a greater inflammatory response is responsible for pathogenesis of severe typhoid, including encephalopathy, the association of age with inflammatory response against typhoid has yet to be investigated in detail.

The Widal test is the oldest and most widely used serologic test for typhoid fever, although its use is complicated by significant cross-reactivity with other *Salmonella* spp. and non-*Salmonella* pathogens and considerable interlaboratory variability. The Widal TH is an agglutination test, primarily representing immunoglobulin G (IgG) directed against the flagella antigen (H antigen) of *Salmonella* Typhi. Our multivariate analysis showed that a Widal TH titer of ≥ 1:640 was independently associated with encephalopathy. However, the Widal TO titer, thought to represent an IgM response against the lipopolysaccharide (O) antigen, was not associated with encephalopathy. It is thought that the TH titer develops after titer of the TO and persists for a longer duration. As such, markedly high TH responses without similarly elevated TO responses during typhoid encephalopathy may reflect previous exposure and prominent amnestic responses to *Salmonella* Typhi.

Other factors that were associated with encephalopathy in this retrospective study were likely a reflection of the increased severity of disease in encephalopathic patients. Severe dehydration was independently associated with encephalopathy, and it may be related to decreased oral intake in the confused patient, a marker of more severe disease and higher insensible losses resulting in circulatory compromise or alternatively, a direct cause of encephalopathy. Of note, we did not find an association with hyper- or hyponatremia and encephalopathy.

Similarly, the low oxygen saturation and high respiratory rate found to be associated with encephalopathy on univariate analysis may be related to a compromised airway in patients with altered mental status, capillary leak in early sepsis, or pneumonia. Leucopenia and thrombocytopenia were also associated with encephalopathy in our analysis, perhaps again reflecting the severity of disease or the effect of *Salmonella* Typhi infection on bone marrow progenitor cells.

Typhoid encephalopathy is thought to occur in the third week of illness, although it is now rare for individuals to remain untreated for this duration. In our study, the median duration of fever did not differ significantly between those patients with (5 days) and without (7 days) encephalopathy. This finding is consistent with a previous report from Indonesia that showed that patients with encephalopathy presented with 7–9 days of symptoms. However, our observation is limited by the inclusion of only culture-positive patients. Because culture yield is thought to decrease over time, we may have missed those patients who presented later in their disease course and were culture-negative.

Of note, we did not find an association of encephalopathy with multidrug-resistant *Salmonella* Typhi, despite drug resistance being associated with higher mortality and morbidity in a study of Pakistani children infected with *Salmonella* Typhi. One of the limitations of this study is that we were unable to assess the colony count, time to culture positivity, and strain type of *Salmonella* Typhi isolated, and it is possible that differences in bacterial burden or virulence play a role in determining central nervous system (CNS) involvement.

The pathogenesis of typhoid encephalopathy remains unknown. *Salmonella* Typhi is rarely found in the CNS, isolated in only 2% of patients with blood culture-positive severe typhoid fever. It has been proposed that steroids decrease mortality in typhoid encephalopathy by reducing the production and release of prostaglandins and free oxygen.

<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.11 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.20–31 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.22 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-1β and TNF-α in the acute phase than those patients with uncomplicated disease.23 IFN-γ cellular responses are also elevated during early typhoid fever, with the majority of this response reflecting CD4 cells.24 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.

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