

Original Research Article

Study of clinico-epidemiological risk factors associated with enteric encephalopathy in children

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ABSTRACT

Background: Although relatively less prevalent, yet enteric encephalopathy is one of the severe complications of enteric fever, which often remains underdiagnosed and undertreated. Data on enteric encephalopathy in children in Indian literature is scarce.

Methods: Current retrospective study was conducted by reviewing the case records of all children admitted with enteric fever between January 2013 and December 2017 in a tertiary health care center. Then the clinical characteristics and laboratory parameters of the subgroup with and without enteric encephalopathy was compared.

Results: Out of the 295 children with enteric fever, 19 children (6.4%) had evidence of enteric encephalopathy during hospital stay. Common clinical presentations were altered sensorium, gait instability, seizure, irrelevant talking and behavioral abnormality. All the children survived after being treated with intravenous dexamethasone along with antibiotics. As compared to the group without encephalopathy, this group had more children with lower socioeconomic status, delayed treatment initiation, malnutrition, higher respiratory rate and heart rate, lower leukocyte and platelet count, higher incidence of hepatic dysfunction, higher *Salmonella typhi* H and O agglutinin titer.

Conclusions: Appropriate clinical suspicion for early diagnosis, timely treatment with dexamethasone and good supportive care is likely to cause favorable outcome in children with enteric encephalopathy.

Keywords: Children, Enteric fever, Encephalopathy, Risk factors

INTRODUCTION

Typhoid fever is a systemic illness caused by infection with *Salmonella typhi* and Paratyphi.¹ It affects over 21 million people each year worldwide, with the highest incidence among infants and children living in south-central and south-east Asia. Initial signs and symptoms include fever, chills, anorexia, malaise, headache, abdominal pain, and constipation.² Although the most-studied complications of severe typhoid fever include intestinal perforation and hemorrhage, numerous

extraintestinal manifestations, including encephalopathy, can occur, especially in severe disease. In accordance with its frequency of occurrence, it comes after hemorrhage and perforation as the third most frequent complication.³ With the advent of better drugs and surgical care, the incidence of intestinal perforation has markedly decreased during recent years. Previously it was proposed, due to prolonged neglect and inadequate care, quite a number of such cases develop hyper-toxaemia leading to meningism and other neurological complications.⁴ However, many times neurological

symptoms develop from the very first week of the illness and other features of marked toxemia may appear later on.⁵ Thus, it would not be correct to say that encephalopathy in enteric fever develops only due to a prolonged period of neglect in treating the case. It is difficult to understand why certain cases develop encephalopathy regardless of whether they are in the first week of illness or in later stages.¹ Few cases of acute disseminated encephalomyelitis even have been explained following enteric fever.⁶ A variety of objective neurologic signs have been documented, apart from acute neuropsychiatric illness in enteric encephalopathy.⁷ In pediatric age group, the data regarding enteric encephalopathy is limited to few case series, especially in Indian subcontinent and these also have no clinical consensus regarding the risk factors and optimum management guidelines. Although dexamethasone has been found to have definitive therapeutic role, further studies are required to formulate optimum management guidelines for this rare complication of enteric fever.

METHODS

The current study was carried out in a tertiary health care centre in New Delhi. After obtaining institute ethics committee approval, all case records of previous five years admitted children less than 18 years were screened and the children who were confirmatory evidence of enteric fever (either by blood culture, serology or other methods) were evaluated. Subsequently the clinical details of these children were reviewed from the case record to determine the clinical evidence of enteric encephalopathy. The clinical presentation, laboratory parameters, neuroimaging findings, treatment protocols used in these children and final outcome including

duration of hospital stay were recorded in a predesigned case record form. Apart from that the clinical profiles of the children with enteric encephalopathy were analyzed to determine association with various risk factors. 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. Authors 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. Authors compared the characteristics of bacteremic patients with evidence of encephalopathy and bacteremic patients without encephalopathy. For continuous variables, authors used the Student t test or the Mann-Whitney U test (for non-parametric data) to compare groups. For categorical variables, authors used Fisher's exact tests. Authors performed statistical analyses using SPSS 17.0 (SPSS Inc., Chicago, IL). Statistical significance was defined as a two-tailed P value <0.05.

RESULTS

During the previous five years before the study (January 2013 to December 2017), 295 children were admitted with a confirmatory diagnosis of enteric fever.

Out of these, 19 children (6.4 %) were found to have enteric encephalopathy i.e. at some time during clinical course had some objective neurological or neuropsychiatric features, without any other reversible or confounding factors establishing the diagnosis of enteric encephalopathy.

Table 1: Comparison of clinical characteristics and laboratory parameters between the subgroup with and without enteric encephalopathy.

Clinical characteristics and laboratory parameters	Subgroup with enteric encephalopathy(n=19)	Subgroup without enteric encephalopathy (n=276)	P-value
Children with delay in antibiotic initiation >7 days	15 (78%)	42 (15%)	0.03
Lower socio-economic status	15 (78%)	51 (18%)	0.03
Malnutrition	15 (78%)	47 (17%)	0.03
Signs of dehydration	14 (73%)	19 ((7%)	0.01
Persistently high respiratory rate above the age range	14 (73%)	31 (11%)	0.02
Persistently high heart rate above the age range	14 (73%)	34 (12%)	0.03
Mean TLC (cells/ul)	4600 (±1300)	6300 (±2200)	0.001
Mean Platelet count(cells/ul)	120000 (±38000)	230000 (±63000)	0.0001
Percentage of children with jaundice and total serum bilirubin >2 mg/dl	15 (78%)	38 (14%)	0.03
Percentage of children with liver transaminase >2 times the upper limit of normal	16 (84%)	46 (16%)	<0.001
S. typhi O agglutinin titer >1:320	10 (52%)	28 (10%)	<0.001
S. typhi H agglutinin titer >1:320	13 (68%)	33 (12%)	0.02
Nalidixic acid resistance	3 (15%)	5 (2%)	0.01

Out of these 19 children, 11 (57%) were boys and 8 children (43%) were girls. Two children (10%) were in age group 2-5 years, 9 children (47%) in the age group 5-10 years and 8 children (42%) in age group 10-18 years. The baseline respiratory rate and heart rate of these children were increased from age appropriate range in 14 children (73%), which was significantly higher as compared to those without encephalopathy. Four children (21%) with enteric encephalopathy required oxygen inhalation and none of them required mechanical ventilation. Comparison of various clinical features and laboratory parameters between the subgroup with and without enteric encephalopathy is illustrated in Table 1.

Most common clinical presentation of encephalopathy was not obeying verbal commands, not indicating basic needs, irrelevant talking or incomprehensible words, excessive irritability or lethargy, aggressive and disruptive behavior, gait instability and seizure (2 children, 10%). Out of the 3 children (15%) with gait instability, all had wide based incoherent gait with frequent falling, swaying from side to side and difficulty taking a turn, indicating cerebellar involvement, although other objective signs of cerebellar involvement were not present in them. None of the children had any focal deficit, cranial nerve palsy, visual abnormality, signs of increased intracranial pressure or papilledema on fundus examination. MRI brain with contrast was done in 15 patients (78%), which were normal and in rest 4 children (22%), CT scan of the brain with contrast was done, which was also normal.

15 children (78%) had high grade fever duration of more than 7 days and had not received any oral antibiotic even before presenting to present institute. All of these children were of lower socioeconomic status, had grade II malnutrition or more and drinking water supplies of most of these children were found to be nonhygienic. 13 children (68%) had clinical icterus and laboratory bilirubin value >2.0 mg/dl. 16 children (84%) had increase in liver transaminase enzymes more than 2 times the upper limit of normal. Mean TLC of these children was 4600/ microliter and mean platelet count was 1, 20, 000, which is less than the corresponding values in the subgroup without encephalopathy. 14 children (73%) had persistent vomiting, accompanied by significant poor oral intake and decreased urine output at least for 48 hours before presenting to present institute. These children also had some signs of dehydration at the time of presentation in the form of sunken eyes, dry tongue, delayed abdominal skin pinch return, oliguria and elevated blood urea and creatinine.

Blood culture was positive for *Salmonella typhi* in 11 children (57%) and all of them were sensitive to cephalosporins and quinolones, however, in 2 children (10%) the isolate was resistant to nalidixic acid. Widal test was positive in all the 19 children done after 1 week of fever onset. *Salmonella typhi* flagellar H agglutinin titer was >1:320 in 13 children (68%) and *Salmonella*

typhi O agglutinin titer was >1:320 in 10 children (52%). Both of these are significantly higher as compared to the group without encephalopathy. The group with encephalopathy had mean duration of hospital stay of 11 days, which was statistically higher significantly than those without encephalopathy. All the children received dexamethasone, within 24 hours of detection of encephalopathy and all had favorable response characterized by improvement in sensorium. All these children were started on injection ceftriaxone initially and 3 children (15%) required further injection ofloxacin in view of persistent fever spikes after one week and worsening clinical status. Only one child had associated intestinal hemorrhage and Malena and required blood product transfusion.

DISCUSSION

In present study, prevalence of enteric encephalopathy was found to be 6.4%, which is lower than that described in studies done in previous decade and earlier.¹ This could be due to improved health care and timely commencement of appropriate treatment, this serious complication of enteric fever is now becoming less prevalent. In current study, the enteric encephalopathy was more prevalent in boys and school age group, which is consistent with results of previous studies by Leung et al.¹ In the current study, other risk factors associated with enteric encephalopathy, interval between fever onset and beginning of treatment, higher respiratory rate and heart rate at the time of clinical presentation, signs of dehydration, low total leukocyte count and platelet count and higher titer >1:320 of H and O agglutinin titer. Previous studies by Leung et al, Parry et al and Khatun et al had also demonstrated in their studies of similar risk factors in children with enteric fever predisposing for encephalopathy.^{3,2} Currently dexamethasone is being used with clinical consensus worldwide for treatment of enteric encephalopathy and in present study, as well as previous studies by Qamar et al, Sagar V et al and Sejvar et al had demonstrated efficacy of dexamethasone in this condition.^{4,8,9} The dose of dexamethasone used in enteric encephalopathy is high upto 1-2 mg/kg/day in divided doses, as mentioned previously by Chisti et al.⁶ Association of other complications like pneumonia and intestinal hemorrhage have been previously shown by Mellon et al.⁷ Khatun et al had previously shown that although the prevalence of MDR typhoid bacilli was not significantly high amongst those with encephalopathy, still nalidixic acid resistance is more common in those with encephalopathy and similar results were also found in present study.²

CONCLUSION

Enteric encephalopathy is one of those rare severe complications associated with this common febrile illness in community, which, if timely treated with dexamethasone can lead to dramatic improvement and complete recovery without any neurological sequelae.

This enigmatic entity still remains underrecognized and underappreciated, especially in pediatric age group. Hence, further larger multicentric clinical studies are required to better elucidate the clinical profile and risk factors of this treatable entity.

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