Research Paper

Factors Associated With Mortality in Toxic Encephalopathy Due to Shigellosis in Children

MACHINARY PUTHENPURAYIL JAYAKRISHNAN[1], MADATHIL GOVINDARAJ GEETA[1], PADINHARATH KRISHNAKUMAR[2], VK GIREESHAN[1], BIJU GEORGE[3], P PRATHIKSHA[4], GOVINDAKARNAVAR ARUNKUMAR[4] AND PM ANITHA[5]

From Departments of [1]Pediatrics, [3]Community Medicine and [5]Microbiology, Government Medical College, Kozhikode, Kerala; [2]Institute of Mental Health and Neurosciences (IMHANS), Kozhikode, Kerala and [4]Manipal Institute of Virology, Manipal Academy of Higher Education (Deemed to be University), Manipal, Karnataka , India.

Correspondence to: *Dr Machinary Puthenpurayil Jayakrishnan, Additional Professor of Pediatrics, Government Medical College, Kozhikode, Kerala, India. mp.jayakrishnan@gmail.com*

PII: S097475591600225

ABSTRACT

Background: There are no reports on factors associated with mortality in Shigella encephalopathy from India. **Objective:** To study the clinical characteristics and factors associated with mortality among children with *Shigella* encephalopathy. **Methods**: The data collection was done prospectively from January, 2018 to May, 2019 with retrospective data from June, 2016 to December, 2017. **Participants:** The study cohort consisted of 58 children <12 years of age with *Shigella* encephalopathy admitted to the Pediatric Intensive Care Unit. **Methods**: *Shigella* encephalopathy was confirmed if culture or real time Polymerase Chain Reaction (PCR) of a stool sample or rectal swab was positive, with temporal association of diarrhea with seizures, altered sensorium or both. Association of mortality with risk factors was tested using chi square test, and the strength of association was estimated in terms of relative risk (RR) and 95% CI. **Results:** Seizures and altered sensorium were the predominant neurological symptoms. Shock occurred in 32 (55%) children, while blood in stools was a feature in only 6 (10%) children. *S.sonnei* was the commonest species identified on stool culture (19;33%). On univariate analysis, prolonged seizures, shock, prolonged altered sensorium, multi - organ dysfunction, lymphocytopenia at admission and need for mechanical ventilation were significantly associated with mortality. On multivariate regression, delayed presentation (presentation to the hospital 48 hours after the onset of symptoms) and prolonged altered sensorium (>12 hours) were found to be independently associated with mortality. **Conclusions:** Recognition of factors associated with mortality in Shigella encephalopathy may assist in better monitoring of sicker children and improved outcomes.

Keywords: *Diarrhea, Ekiri syndrome, Morbidity, Outcome, S. sonnei.*

Shigellosis continues to be an important cause of diarrhea-related mortality in developing countries [1,2] with *S. flexneri being* the predominant species endemic in India [3]. The most common extra-intestinal complication in shigellosis is encephalopathy, presenting with seizures, headache, lethargy, confusion or hallucinations [4]. Over the last few decades, there has been a substantial reduction in deaths related to shigellosis [5]. Children with *Shigella* encephalopathy usually recover without any neurological deficits [4].

A recent study from Bangladesh has reported high case fatality in children with *Shigella* encephalopathy [6] We have also noticed an increase in mortality due to *Shigella* encephalopathy in our center which prompted us to analyze the hospital records which showed that there was only one death between 2013 and 2015 (unpublished data). Lethal toxic encephalopathy or Ekiri syndrome (a severe form of encephalopathy resulting in rapid progression to coma and death) is reported in children with shigellosis from abroad but not from India [7]. The present study aimed to describe the clinical characteristics of *Shigella* encephalopathy in children and to identify factors associated with mortality.

METHODS

The study was conducted in the Pediatric Intensive Care Unit (PICU) of the Government Medical College, Kozhikode, a tertiary referral centre. Children between 1 month and 12 years of age admitted from 1 June, 2016 to 31 May, 2019 with a diagnosis of *Shigella* encephalopathy were included in the study. The data col-

lection was done prospectively from January, 2018 to May, 2019 with retrospective data from June, 2016 to December, 2017. The study was approved by the institutional ethics committee.

Shigella encephalopathy was suspected based on the temporal association of diarrhea with altered sensorium, seizures or both in children. Stool microscopy and culture were done in all cases, apart from other investigations including complete blood count, blood culture, cerebrospinal fluid analysis and culture, blood sugar, serum electrolytes, renal and liver function tests. The diagnosis was confirmed if *Shigella* spp. was isolated from a stool sample or rectal swab, or if polymerase chain reaction (PCR) from a stool sample was positive. Children with a negative stool culture or PCR, history of seizures poorly controlled with antiepileptics, and those whose sensorium improved after correction of shock were excluded from the study.

The clinical characteristics were recorded and the factors associated with mortality were studied. The following definitions were chosen: Delayed presentation: Presentation to the hospital 48 hours after the onset of symptoms; Undernutrition: weight for age or weight for height below -2 z-scores on the WHO child growth standards; Fluid refractory shock: persistent shock despite administration of 60 ml/kg of fluid in first hour or development of fluid overload features like hepatomegaly or lung crepitations; Multi organ dysfunction: dysfunction of 2 or more organ systems other than the CNS; Prolonged seizure: seizures lasting for more than 30 minutes without the child regaining consciousness in between; Prolonged altered sensorium: altered sensorium lasting more than 12 hours; Hyponatremia: serum sodium concentration less than 135 mmol/L; Hypocalcemia: serum ionized calcium less than 1.1 mmol/L; Lymphocytopenia: Lymphocyte count below the normative value for the corresponding age.

All children were treated with ceftriaxone and other supportive measures, which included management of seizures and raised intracranial tension. Indications for mechanical ventilation included worsening respiratory failure, refractory shock and a score on the Glasgow coma scale of <8. Seizures were managed in accordance with the unit protocol which included a benzodiazepine, followed by fosphenytoin and levetiracetam or sodium valproate, depending on the response. Hypertonic saline (3%) was used as therapy for raised intracranial tension. Shock was managed as per standard protocol, including fluid boluses and inotropic support in fluid refractory shock. Appropriate intravenous fluids were used for rehydration and replacement of ongoing losses.

Statistical analysis: Qualitative variables were summarised as frequency and percentages and association of mortality with risk factors were tested using chi square test. A P value of < 0.05 was considered to be statistically significant. Strength of association of risk factors with mortality was estimated in terms of relative risk (RR) and its 95% confidence interval (95% CI). A multivariate logistic regression was done to find out adjusted odds ratio of the variables. Those variables which were found to be significant on univariate analysis were selected for modeling using binary logistic regression to obtain an adjusted OR and its 95% CI. Statistical analysis was performed using SPSS V.16 (SPSS, Chicago, Illinois, USA).

RESULTS

Out of 158 probable cases, *Shigella* encephalopathy was confirmed in 60 children.

Among them 2 children had epilepsy with poorly controlled seizures and were not included for the analysis. The final sample consisted *of* 58 children with confirmed schigella encephaloathy.The prospective and

retrospective data included 40 and 18 children respectively. There were 27 girls and 31 boys. Stool culture was positive for Shigella in 23 (40%) children while the rest had stool PCR positive for *Shigella* spp.

Nearly half (48%) of the diarrheal episodes occurred during the months of May and June. All except 5 children (53; 91%) were admitted to the PICU within 48 hours, and 45 (78%) of them on the first day of illness itself. The initial symptom was fever in 54 (93%) children and seizures, loose stools, vomiting and abdominal pain in one child each. Seizures and altered sensorium were the predominant neurological symptoms. Altered sensorium or seizures preceded loose stools in 16 (28%) children, while the majority (42; 72%) developed features of encephalopathy after the onset of loose stools (***Table* I**). *S. sonnei* was the commonest organism identified in stool culture (33%) followed by *S.boydii* (3%) and S.*flexneri* (2%). Blood culture was sterile in all cases.

The mortality in the present sample was 26%. More than half (9;60%) of the children who died were below the age of 5 years. Death occurred within 24 hours of hospitalization in (4, 27%) children and within 48 hours in 7 (47%) children. All 5 children who were admitted after 48 hours of onset died.

Among the children who died, prolonged altered sensorium occurred in 13 (87%), while 7 (47%) children had prolonged seizures. All the 13 children who had persistent low scores of < 8 on the Glasgow coma scale died. Severe metabolic acidosis in the absence of shock or kidney injury was a feature in 2 (3%) children, and global developmental delay were present in 4 (7%) children. Computed tomography scans of the brain in two children and autopsy in one child showed severe cerebral edema. Stool culture for *S. Sonnei* was positive in 3 children who died.

On univariate analysis, prolonged seizures, admission to PICU after 48 hours of onset, shock, prolonged altered sensorium, persistently low score on the Glasgow coma scale, hyperglycemia at admission, multi - organ dysfunction, need for mechanical ventilation and lymphocytopenia at admission were significantly associated with mortality. On multivariate regression, delayed presentation to the hospital more than 2 days after the onset of any symptoms and altered sensorium for > 12 hours were found to be independently associated with mortality (***Table* II**),

DISCUSSION

We studied the clinical characteristics and mortality in 58 children with *Shigella* encephalopathy during a period of three years. More than a quarter of the children died, possibly due to the occurrence of lethal toxic encephalopathy.Lethal toxic encephalopathy or Ekiri syndrome, first reported from Japan is a rapidly progressing fulminant encephalopathy associated with shigellosis in children [7-8]. In the present sample, children who died had a similar progress of encephalopathy with death occurring within 48 hours of the onset of the disease in 47% of cases.

The cause of death in lethal toxic encephalopathy is not yet well understood, although severe cerebral edema has been described and it is suggested that prevention will help to improve the outcome [7,9]. Entry of inflammatory cytokines into the brain in susceptible children, might be the reason for severe encephalopathy [10]. Our findings are also suggestive of the role of cerebral oedema.

In a large series from Israel, a disproportionate number of cases had developmental delay and intellectual disability, suggesting a possible increased susceptibility [9], though, we could not confirm the

association. Although hypocalcemia and hyponatremia have been reported in children who died due to encephalopathy, they were not significantly associated with mortality in our series [7,9].

S.sonnei was the commonest serogroup isolated in our series, although *S.flexneri* has been reported as the most common serogroup in India [11-13]. Recent studies have reported increasing incidence of S.*sonnei* infections in this region [14]. A shift towards *S.sonnei* has been observed in other countries as socioeconomic conditions improve [15]. A significant association of *S.sonnei* with encephalopathy has been reported earlier, suggesting increased virulence and might partly explain the increased mortality [6].

Delayed presentation and prolonged altered sensorium were found to be independently associated with mortality, suggesting that timely initiation of antibiotics shortens the duration of illness and results in bacteriological clearance, as reported in literature [16]. One limitation of the present study is that the exact cause of rapidly progressing encephalopathy leading to death could not be identified in all children since we could not carry out brain imaging studies in all children and autopsy could be done in one child only.

The increased mortality in shigella encephalopathy in the present sample underscores the need for further studies on the changing virulence of *Shigella* organisms, as well as host-specific risk factors and optimal treatment.

Ethics Clearance: Institutional ethics committee of the Government Medical College, Kozhikode; No. GMCKKD/RP2018/IEC/15 dated 11th January 2018.

Contributors: MPJ: designed study, collected the data and wrote the initial draft of the paper; MGG, PK: helped in writing the manuscript and interpretation of the data; VKG: patient management and helped in collection of the data; BG: expert in statistics who did the statistical analysis; PP, GA,PMA: conducted microbiological analysis.

Funding: None; *Competing interest*: None stated.

What This Study Adds?

- Delayed presentation more than 48 hours after the onset and prolonged altered sensorium beyond 12 hours were the risk factors identified for mortality in *Shigella* encephalopathy in children.

REFERENCES

1. Troeger C, Blacker BF, Khalil IA, Rao PC, Cao S, Zimsen SR, *et al*.GBD 2016 Diarrhoeal Disease Collaborators. Estimates of the global, regional, and national morbidity, mortality, and etiologies of diarrhea in 195 countries: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018;18:1211-8.
2. Khalil IA, Troeger C, Blacker BF, Rao PC, Brown A, Atherly DE, *et al*. Morbidity and mortality due to shigella and enterotoxigenic Escherichia coli diarrhoea: The Global Burden of Disease Study. 1990-2016. Lancet Infect Dis. 2018;18:1229-40.
3. Taneja N, Mewara A Shigellosis: Epidemiology in India. Indian J Med Res. 2016;143: 565-76.
4. Ashkenazi S, Dinari G, Zevulunov A, Nitzan M. Convulsions in childhood shigellosis: Clinical and laboratory features in 153 children. Am J Dis Child. 1987;141:208-10.
5. Bardhan P, Faruque AS, Naheed A, Sack DA. Decrease in shigellosis-related deaths without Shigella spp.-specific interventions, Asia. Emerg Infect Dis. 2010;16: 1718-23.
6. Afroze F, Ahmed T, Sarmin M, Smsb Shahid A, Shahunja KM, ShahrinL, *et al*. Risk factors and outcome of Shigella encephalopathy in Bangladeshi children. PLoS Negl Trop Dis. 2017;11:e0005561.
7. Pourakbari B, Mamishi S, Kohan L, Sedighi L, Mahmoudi S, Fattahi F, *et al*. Lethal toxic encephalopathy due to childhood shigellosis or Ekiri syndrome. J Microbiol, Immunology and Infection. 2012;45:147-50.
8. Sakamoto A, Kamo S. Clinical, statistical observations on ekiri and bacillary dysentery; a study of 785 cases. Ann Paediatr. 1956;186:1-18.
9. Goren A, Freier S, Passwell JH. Lethal toxic encephalopathy due to childhood shigellosis in a developed country. Pediatrics. 1992;89:1189-93.
10. Yuhas Y, Weizman A, Ashkenazi S. Bidirectional concentration-dependent effects of tumor necrosis factor alpha in Shigella dysenteriae-related seizures. Infection and immunity. 2003;71:2288- 91.
11. Mandal J, Ganesh V, Emelda J, Mahadevan S, Parija SC. The recent trends of shigellosis: A JIPMER perspective. J Clin Diagn Res. 2012; 6:1474-7.
12. Ballal M, Devadas SM, Chakraborty R, Shetty V. Emerging trends in the etiology and antimicrobial susceptibility pattern of enteric pathogens in rural Coastal India. Int J Clin Med. 2014;5:425-32.
13. Tejashree A, Vijaykumar GS, Rao R, Mahale RP, Gopalakrishnan R, Ponna Y. Spectrum of enteric pathogens in a tertiary hospital. Transworld Med J. 2013;1:69-73.
14. Madhavan A, Balakrishnan S, Vasudeva panicker J. Antibiotic susceptibility pattern of Shigella isolates in a tertiary healthcare center.J Lab Physicians. 2018;10:140-4.
15. Vinh H, Nhu NT, Nga TV, Duy PT, Campbell JI, Hoang NV, *et al*. A changing picture of shigellosis in Southern Vietnam: Shifting species dominance, antimicrobial susceptibility and clinical presentation. BMC Infect Dis. 2009;9:204.
16. Christopher PR, David KV, John SM, Sankarapandian V. Antibiotic therapy for Shigella dysentery. Cochrane Database Syst Rev. 2010;8:CD006784.

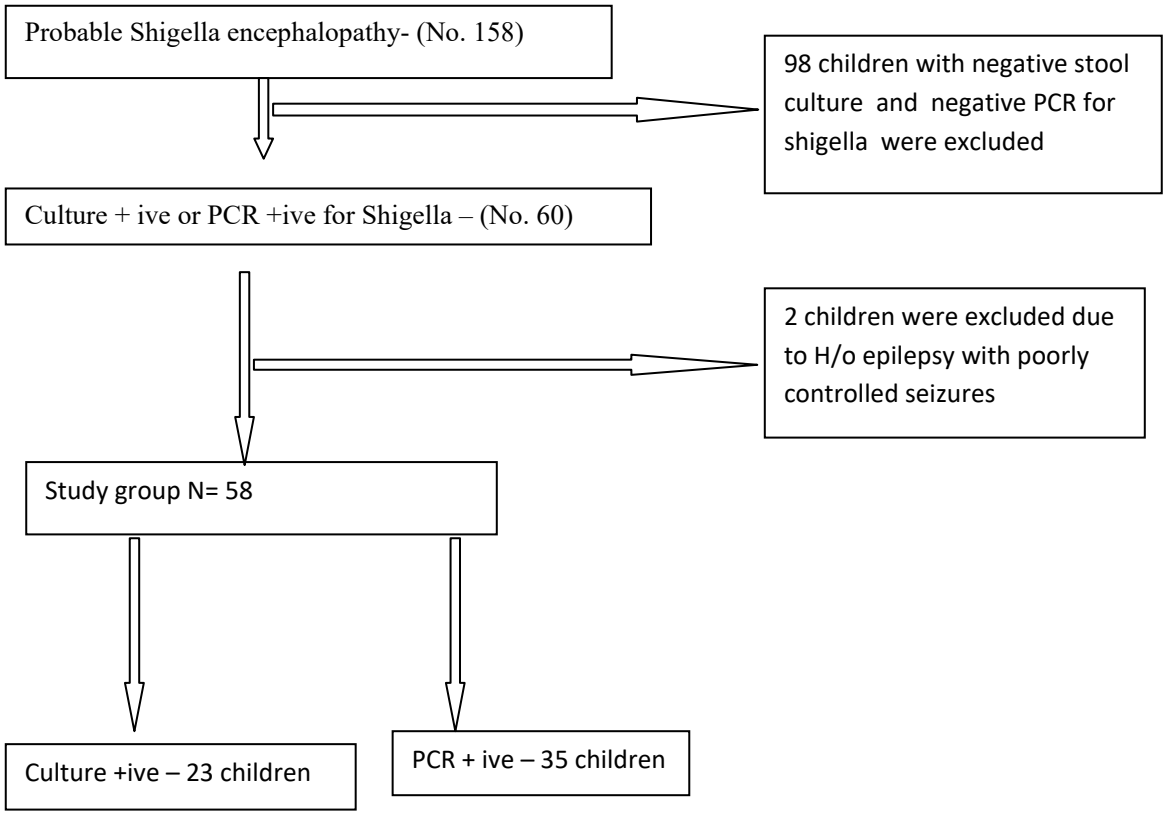
Table I Clinical and Laboratory Characteristics of Children with Shigella Encephalopathy (*N*=58)

Characteristic	*No (%)*
Fever as initial symptom	54(93)
Seizures	51(88)
Prolonged seizure (lasting >30 min)	10 (17)
Altered sensorium	27 (47)
Prolonged altered sensorium (lasting >12 h)	21 (36)
Headache	3 (5)
Blood in stools	6 (10)
Shock	32 (55)
Fluid-refractory shock	25 (43)
Lymphocytopenia	37 (64)
Hypocalcemia	12 (21)
Hyponatremia	28 (48)
Need for mechanical ventilation	13 (22)
Multi-organ dysfunction	11 (19)

Table II Risk Factors for Mortality in Shigella Encephalopathy in Children (*N*=15)

Variables	Adjusted OR 95% CI	*P* value
Prolonged altered sensorium (*n*=13)	18.23 (2.27 to 16.13)	0.006
Hyperglycemia at admission (*n*=4)	1.43 (0.09 to 21.16)	0.79
Shock (*n*=13)	4.64 (0.41 to 52.47)	0.22
Hyponatremia at admission (*n*=5)	0.46 (0.07 to 3.06)	0.42
Undernutrition (*n*=2)	13.13 (0.01 to 17042.92)	0.48
Lymphocytopenia at admis-sion (*n*=5)	0.22 (0.03 to 1.61)	0.14
Delayed presentation to the hospital (*n*=5)	8.74 (1.02 to 74.96)	0.05

Cox and Snell R^2 value = 0.46


Probable Shigella encephalopathy- (No. 158)
98 children with negative stool culture and negative PCR for shigella were excluded
Culture + ive or PCR +ive for Shigella – (No. 60)
2 children were excluded due to H/o epilepsy with poorly controlled seizures
Study group N= 58
Culture +ive – 23 children
PCR + ive – 35 children