



BRIEF COMMUNICATION

# Lethal toxic encephalopathy due to childhood shigellosis or Ekiri syndrome

Babak Pourakbari <sup>a,b</sup>, Setareh Mamishi <sup>a,\*</sup>, Leila Kohan <sup>c</sup>, Leila Sedighi <sup>d</sup>, Shima Mahmoudi <sup>a</sup>, Fatemeh Fattahi <sup>d</sup>, Mostafa Teymuri <sup>a</sup>

<sup>a</sup> Pediatric Infectious Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>b</sup> Department of Microbiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

<sup>c</sup> School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

<sup>d</sup> Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran

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## KEYWORDS

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Lethal toxic encephalopathy due to shigellosis or Ekiri syndrome is a rare complication of shigellosis with a high fatality rate. Data are very limited on factors that can predict this encephalopathy, so we evaluated clinical and laboratory characteristics for these patients. In this study children with extreme toxicity and convulsions followed by rapid neurological deterioration resulting in brain edema and fatal outcome without sepsis and severe dehydration were selected as having lethal toxic encephalopathy. There were 1295 children with shigellosis during the 10 years of the study. Five children (0.4%) had lethal toxic encephalopathy due to shigellosis. Death occurred following rapid neurological deterioration resulting in brain edema despite intensive treatment. Evidence of brain edema may be a prediction factor for death. Early recognition of encephalopathy and measures to prevent brain edema may improve patient outcome. Copyright © 2011, Taiwan Society of Microbiology. Published by Elsevier Taiwan LLC. All rights reserved.

## Introduction

Shigellosis is a common infectious disease that results in considerable morbidity and mortality, especially in

underdeveloped countries. Almost two-thirds of worldwide shigellosis occurs in children, and 99% in developing countries.<sup>1</sup> The morbidity and mortality are predominantly due to extraintestinal complications, especially in *Shigella* encephalopathy, a serious neurologic complication often manifest as altered consciousness, seizures, and coma.<sup>2,3</sup>

Neurological complications, particularly seizures followed by encephalopathy and hallucinations, are among the most common extraintestinal manifestations of shigellosis, with a prevalence of 12–45% in children.<sup>4,5</sup> Peripheral

\* Corresponding author. Department of Pediatric Infectious Diseases, Children's Medical Center Hospital, School of Medicine, Tehran University of Medical Sciences, 62 Gharib St., Keshavarz Blvd., Tehran, Iran.

E-mail address: [smamishi@sina.tums.ac.ir](mailto:smamishi@sina.tums.ac.ir) (S. Mamishi).

neuritis is a rare complication reported mainly in adult patients.<sup>6</sup> In the minority of patients, encephalopathy may be severe, unresponsive to antibiotic therapy, and fatal, even in developed countries.<sup>7</sup> A particular form of lethal toxic encephalopathy due to shigellosis is characterized by rapid onset of neurological abnormalities with only mild colitis. It was first described in Japanese patients during the first half of previous century and named the Ekiri syndrome.<sup>8,9</sup>

Early recognition of lethal toxic encephalopathy using prediction factors might improve patient outcome. Simple clinical and sociodemographic characteristics might play a role in predicting patient prognosis instead of focusing on typing different *Shigella* species. Data are very limited on such prediction factors, although a number of studies have attempted to evaluate the clinical and laboratory characteristics of such children.<sup>3,7,9</sup> In this study we describe five children who presented with lethal toxic encephalopathy state due to shigellosis or Ekiri syndrome.

## Patients and methods

This retrospective study was conducted at the Children's Medical Center Hospital, Tehran, Iran. We reviewed the medical records of all hospitalized children for whom *Shigella* spp. was isolated from a stool sample during 1999–2008. Among these patients, children with extreme toxicity, convulsions, and hyperpyrexia followed by rapid neurological deterioration resulting in brain edema and fatal outcome without sepsis and severe dehydration were selected as having lethal toxic encephalopathy due to shigellosis. Information obtained from the patient records included age, sex, symptoms (fever, vomiting, diarrhea) prior to hospitalization, and clinical course. Information from the physical examination included general condition, fever, abdominal examination, quality of stool (water, mucus, blood), and neurological status. Admission laboratory information included blood cell count, levels of serum electrolytes, *Shigella* spp. isolates from stool cultures, and antibiotic sensitivity results. Computed tomography was also carried out if it was available.

## Results

During this 10-year study, 1295 children ranging in age from 1.5 months to 13 years with shigellosis were hospitalized in the Children's Medical Center Hospital. There were 680 (52.5%) boys and 615 (47.5%) girls. Most of the patients (62.3%) were admitted to the hospital during spring and summer. Five children (0.4%) with a mean age of 7.1 years had lethal encephalopathy due to shigellosis. Age and sex data for the five cases are shown in Table 1. All of the patients were well-nourished healthy children prior to their illness. Their previous medical history was unremarkable. They had no neurological disorders and head trauma, and use of possible culpable medication was ruled out. No one in their immediate surroundings had diarrhea.

All cases were admitted to hospital with a history of fever, abdominal pain, recurrent vomiting, and the passage of frequent brownish and later green diarrhea without

blood or mucus. Illness duration prior to hospitalization was 2 days for Cases 1, 2, and 3, 1 day for Case 4, and 7 days for Case 5. All cases had one episode of tonic–clonic seizure before admission that was controlled using diazepam in another center. On arrival in the pediatric emergency department, Cases 1, 3, and 4 were unconscious. Examination data, including blood pressure, pulse rate, respiratory rate, and temperature, are shown in Table 1. Cases 1 and 2 had severe hyperpyrexia. There were signs of mild to moderate dehydration in all cases. Glasgow coma scores were estimated as six for Cases 3, 4 and 5, and three for Cases 1 and 2. Other physical examination results were normal. All cases were referred to the intensive care unit for further diagnostic evaluation and therapy.

Stool samples from all cases were cultured. Two cases had *S. flexneri* in their stool, and samples from the other three failed to agglutinate with *Shigella* spp. typing sera (Table 1). Laboratory data are shown in Table 1. There was severe neutropenia in Cases 1 and 3, and thrombocytopenia in Case 3. Hyponatremia was seen in all cases. There were calcium and potassium derangements in Cases 3 and 4.

Although there was clinical evidence of brain edema in all cases, computed tomography of the brain was performed only in one case because the other cases were unstable. This revealed brain edema.

Dehydration and electrolytes derangements were managed, and ceftriaxone was initiated in all cases. Hyperventilation and mannitol were provided to treat the brain edema. In spite of intensive treatment, the clinical situation of the cases dramatically deteriorated and resulted in their death.

Antibiotic susceptibility to ceftriaxone, nalidixic acid amikacin was determined (Table 1). *S. flexneri* isolates from Cases 1 and 3 were most sensitive to nalidixic acid. Isolates from Case 3 were sensitive to amikacin.

## Discussion

This study reports five cases of fatal shigellosis during a period of 10 years. From rapidly developing seizures and altered consciousness followed by intestinal symptoms and fever attributed to *Shigella* spp. infection, lethal toxic encephalopathy or Ekiri syndrome was diagnosed. Death in all cases occurred following rapid neurological deterioration that resulted in brain edema.

In our study all of the cases had seizures and three of them were unconscious on arrival. In a previous study on childhood shigellosis, being unconscious or having seizures was strongly associated with death, but it is unclear if seizures are simply a marker for more severe disease or seizures actually contribute to death.<sup>10</sup>

A number of studies have reported lethal toxic encephalopathy due to shigellosis in the past few years.<sup>2,3,7,9,11</sup> One study reported three cases aged 9–11 years who showed a typical encephalopathic clinical and pathological pattern due to *S. flexneri*.<sup>2</sup> Another report involved a 3.5-year-old child who had encephalopathy and "Reye-like" metabolic derangement due to *S. flexneri*.<sup>12</sup> In the largest series, 15 patients aged 5 months to 11 years died following shigellosis in a 10-year period.<sup>3</sup> The cause of death in all patients was consistent with toxic encephalopathy and

**Table 1** Clinical characteristics and laboratory findings at the time of admission for five cases of lethal encephalopathy due to shigellosis

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Female	Female	Male	Male	Female
Age (Y)	11	5	4	4	3.5
Temperature (°C)	39	39.5	38.2	38.5	37.5
WBC (/mm <sup>3</sup> )	2000	6300	1000	5300	4700
Platelets (/mm <sup>3</sup> )	175,000	155,000	102,000	224,000	188,000
Na (meq/L)	130	132	126	133	133
K (meq/L)	3.9	3.5	3.1	2.3	3.9
Calcium (meq/L)	9	10.2	8	8.4	9
Stool RBC (/field)	>50	—	5–7	10–12	—
Stool WBC (/field)	>50	—	3–4	>50	—
Stool culture	<i>S. flexneri</i>	<i>Shigella</i> spp.	<i>S. flexneri</i>	<i>Shigella</i> spp.	<i>Shigella</i> spp.
Antibiotic sensitivity	Nalidixic acid	Ceftriaxone	Nalidixic acid and amikacin	—	—

RBC = Red Blood Cell; WBC = White Blood Cell.

*Shigella* spp. included *S. flexneri*, *S. sonnei*, and *S. dysenteriae*. Only headache was a prominent feature of patients who died. In our study, two cases had *S. flexneri* in stool samples and agglutination with *Shigella* typing sera was negative for samples from the other three cases. In a recent study, the most common species of *Shigella* in Iranian children were *S. flexneri* (48%) and *S. sonnei* (45%).<sup>13</sup>

The pathogenesis of lethal encephalopathy due to shigellosis or Ekiri remains unknown. It has been postulated that Shiga toxin, which is only produced by *Shigella dysenteriae* type 1, plays a role.<sup>4,14</sup> However, the other three *Shigella* species that have been isolated from infants usually do not produce the toxin. In our study, two cases had *S. flexneri*. Thus, Shiga toxin production may be not essential for this lethal complication,<sup>2,15</sup> often associated with brain edema or hemorrhage.<sup>2</sup> Previous studies suggested that brain edema occurs in patients with shigellosis and lethal toxic encephalopathy.<sup>2,3,5,7,9,11</sup> In our study, all cases had clinical evidence of brain edema, and computed tomography in one case confirmed this. Thus, evidence of brain edema may be useful as a prediction factor for fatal outcome.

It is possible that the premorbid state (mental retardation, coinfection) or metabolic abnormalities have no influence. Hypocalcemia was considered to have a pathogenic role in Japanese children with Ekiri.<sup>9</sup> The authors suggested that dietary supplementation with calcium might reduce the incidence of Ekiri. However, signs of central nervous system involvement and circulatory collapse remained in a patient with Ekiri given calcium therapy.<sup>9</sup> In our study, two cases had mild hypocalcemia, but this is considered insignificant in the pathogenesis of lethal encephalopathy. Hyponatremia was seen in all cases in this study. Although previous studies on shigellosis reported hyponatremia in association with seizures, they did not identify this as a risk factor for the development of seizures.<sup>5</sup> A number of studies on lethal encephalopathy due to shigellosis found hyponatremia,<sup>3,7</sup> but hyponatremia was not considered significant in the pathogenesis of this neurological catastrophe.

The ability of antibiotic treatment to prevent serious complications due to shigellosis has not been proven.<sup>2,4,5</sup> In

one case of a 3-year-old child with encephalopathy due to shigellosis, empiric initiation of ceftriaxone, dexamethasone, and acyclovir was effective and the child survived.<sup>7</sup> In our study, intensive treatment was not successful which may be due to a resistant organism or delayed initiation of treatment. Increased *Shigella* spp. resistance has been observed in Iranian children.<sup>16</sup> Early introduction of appropriate antimicrobial treatment in a could help solving this question. *S. flexneri* from Cases 1 and 3 in our study was sensitive to nalidixic acid, which is still one of the most appropriate antibiotics for treatment of shigellosis due to *Shigella* spp. especially *S. flexneri*.<sup>13</sup>

In summary, this study reported five cases of lethal toxic encephalopathy associated with shigellosis or Ekiri syndrome. Death occurred following rapid neurological deterioration resulting in brain edema despite intensive treatment. Evidence of brain edema may be a prediction factor for death. Early recognition of encephalopathy and measures to prevent brain edema may improve patient outcome.

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