Paediatr Croat. 2012;56:261-263

FULMINATING SHIGELLA ENCEPHALOPATHY (EKIRI SYNDROME)

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Complications of shigella infection include both intestinal and extraintestinal manifestations. Hemolytic uremic syndrome and central nervous system complications are among the most common extraintestinal manifestations of shigellosis. Neurological manifestation, particularly seizures and encephalopathy, are not common in childhood shigellosis. Brain edema is a common finding in patients presenting with severe shigella encephalopathy. Shiga toxin production is not essential for development of shigella associated neurological symptoms. Early recognition and proper management of cases of severe shigella encephalopathy may help improve the outcome. A case is reported of a 2.5-year-old female child with severe fulminating shigella encephalopathy (ekiri syndrome) who achieved complete recovery. Brain computed tomography findings of this patient are presented.

Descriptors: SEIZURES; BRAIN EDEMA; SYNDROME; DYSENTERY, BACILLARY; CHILD, PRESCHOOL

CASE REPORT

A 2.5-year-old child was admitted to the emergency ward with high fever (38.5-39.5°C), generalized tonic-clonic seizure attack, drowsiness, vomiting and diarrhea, with no signs of dehydration. Soon, the child developed second seizure episodes, 10 minutes apart; both were aborted by intravenous (iv.) diazepam and she was kept on continuous phenobarbital infusion. The child suddenly developed cardiorespiratory arrest. She was immediately resuscitated and supported with mechanical ventilation. After 2 days, the state of consciousness improved. The child was extubated on day 3 of admission, following improvement of consciousness and beginning of spontaneous respiratory movements.

Differential diagnosis included infections of the central nervous system (CNS; meningitis, meningitis-encephalitis) and febrile convulsion.

All test results for blood, urine, stool and cerebrospinal fluid samples were normal except for serum sodium (119 mmol/L: 129 mmol/L) and stool examination (many red blood cells). Toxicology screening was negative. Serology study for viruses was also negative. C-reactive protein was 84 mg/dL. Complete blood count results were within the normal range (white blood cell, red blood cell, hemoglobin and platelet count). Blood chemistry test results including calcium and magnesium were within the normal limits. The result of stool culture indicated growth of *Shigella (S.) flexneri* and shigella-associated encephalopathy was assumed.

Neurological examination was normal, with no focal findings. Electroencephalogram showed slow background activity with slow sharp waves. Brain computed tomography (CT) showed generalized brain edema.

Ekiri syndrome was diagnosed in this patient according to the general course of the disease, brain edema, hyponatremia, absence of dehydration and positive stool culture for *S. flexneri*.

She was treated with anticonvulsants due to recurrent seizures and ceftriaxone, for the probability of shigellosis. Fluids were administered at two-thirds of the maintenance dose because the patient had no signs of dehydration.

Hyponatremia correction was performed in such a way that the values of sodium would not exceed 0.5.mEq/L *per* hour. For generalized brain edema, the patient was treated with iv. mannitol, dexamethasone and hyperventilation.

DISCUSSION

Today, despite numerous prophylaxis precautions and use of new antibiotics, shigellosis remains an important problem in both developed and developing countries (1-3). The incidence of shigellosis is estimated to 164.7 million cases *per* year throughout the world. Developing countries are at a high risk with 163.7 million cases a year, including 1.1 million deaths a year. Approximately 60% of all cases and 61% of all deaths are caused by shigellosis, noted in children up to five years old. Developing countries have a ratio of 20-fold higher incidence compared to developed countries. Although the relative importance of different serotypes is unknown, about 30% of the infections are due to *S. dysenteriae* (1, 2). In industrialized societies, *S. sonnei* is the most common cause of bacillary dysentery, with *S. flexneri* second in frequency; in preindustrial societies, *S. flexneri* is most common, with *S. sonnei* second in frequency (5-7).

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The risk factors responsible for shigella infections are related to unsuitable hygienic conditions. Contaminated food and water are the most important vectors. Person-to-person transmission also remains an important element. The strongest risk factor for shigella encephalopathy was early stopping of breastfeeding. Breastfeeding decreases the risk of symptomatic shigellosis and lessens its severity in those infants who acquire infection despite breastfeeding (1, 2, 6, 7). For travelers who visit endemic areas for short periods, prophylaxis against traveler's diarrhea has been recommended by some. Currently, no licensed vaccines targeting *shigella* or enterotoxigenic *Escherichia coli* (ETEC) exist; however, vaccines against both bacteria are being developed (7, 8).

Complications of shigella infection include both intestinal and extraintestinal manifestations (2).

Hemolytic uremic syndrome and CNS complications are among the most common extraintestinal manifestations of fatal shigellosis (1, 4). Convulsions and transient acute encephalopathy (which is characterized by seizures, headaches, lethargy, confusion, alterations in mental status) are the most common neurological manifestations reported in the pediatric age (1, 3). More than 25%-40% of children hospitalized with shigellosis infection develop neurological manifestations as extraintestinal complications (1).

We present this case and the clinical aspect of ekiri syndrome to draw attention to its presence as a complication of shigellosis infection and to show that in rare cases it can have a good outcome.

Identification of the clinical signs of a shigella infection, along with due attention paid to the nervous system, in the absence of viral and bacterial infections of the CNS, will help diagnosing ekiri syndrome. In these conditions, image examinations such as CT or MRI will identify the presence of cerebral edema, adding another diagnostic criteria for the ekiri syndrome (8, 9). Orientation and an early diagnosis as well as immediate initiation of treatment will help improve the patient's condition. This could be a factor contributing to favorable outcome.

Cases with good outcome have been reported in different pediatric age groups (i.e. 3, 4, 6.5 years), with description of their clinical presentation, laboratory data and images of the ekiri syndrome (8-10). After analyzing the prognostic factors that affected the outcome in children with ekiri syndrome, the authors argue that if it is not possible to find the possible reason of survival in these patients, it can be postulated that the timely diagnosis and differential diagnosis enabled early introduction of appropriate therapy for cerebral edema and prescribing of antimicrobial medication leading to better health performance.

According to them, there are similar reports of patients with the shigella syndrome infection worsened by ekiri syndrome, clinically first presented with encephalopathy and cerebral edema without gastrointestinal symptoms, who were empirically treated with ceftriaxone, dexamethasone and acyclovir, prior to positive coproculture test results, and with better outcome (11).

On the other hand, cases of ekiri syndrome, in particular with fatal outcome, have been ever less frequently recorded. Shigellosis accompanied by encephalopathy syndrome, known as ekiri (Japanese: epidemic diarrhea), was for the first time recorded by the Japanese (during World War II), where around 15,000 cases of deaths of pediatric patients from ekiri syndrome were identified (12, 13).

Goren et al. studied 15 cases of ekiri syndrome with fatal outcome during the 1980-1990 period (13). In a study including 173 patients with shigella infection, nine (5.2%) patients died from ekiri syndrome and sepsis manifestation despite antimicrobial treatment (10).

Some authors believe that the prognostic factors leading to fatal outcome may be related to the duration of convulsions in terms of convulsive status, the presence of coma, difficulty in establishing the diagnosis, later therapy initiation, etc. Late diagnosis may be related to the fact that some patients with shigella infection present with the symptoms of CNS involvement including decreased consciousness level and seizures (10-12), and sometimes lethal toxic encephalopathy of shigellosis can be the only manifestation of the disease in the absence of intestinal and metabolic symptoms. These may accompany or even precede the development of intestinal symptoms. The case may be misdiagnosed as a primary CNS disease, if neurological symptoms appeared first.

CNS symptoms include severe headache, lethargy, meningitis, delirium, and convulsions lasting less than 15 minutes, especially with *S. dysentery (13, 14)*. Cerebral edema as a common finding of the clinical aspect of ekiri syndrome is found not only on CT but also on autopsy (2, 7, 8).

The pathogenesis of neurological manifestations, especially ekiri syndrome, during shigellosis is not well understood. In the past, these symptoms were attributed to the neurotoxicity of Shiga toxin, in an animal model, but it is clear that this explanation was wrong since the organisms isolated from children with shigella-related seizures are usually not Shiga toxin producers (9, 10, 23, 24). Balter et al. studied the role of nitric oxide in shigella-related seizure in an animal model. Nitric oxide is an important neurotransmitter in both peripheral and central nervous system. Overproduction of nitric oxide has been linked to neurotoxicity during ischemia. It also has a role in some form of neurodegenerative brain disease and in seizure induction (20, 24).

The majority of shigella associated neurological findings have been reported in patients with *S. sonnei* and *S. flexneri*. Both species do not usually produce Shiga toxin, as both are lacking the structural gene encoding Shiga toxin production (2, 13, 20, 21).

CONCLUSION

Early recognition of ekiri syndrome as a complication of shigellosis in pediatric age and aggressive medical treatment of cerebral edema can contribute to favorable prognosis of these patients.

Autori izjavljuju da nisu bili u sukobu interesa.
Authors declare no conflict of interest.

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S a ž e t a k

FULMINANTNA ENCEFALOPATIJA UZROKOVANA ŠIGELOM (SINDROM EKIRI)

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Komplikacije uzrokovane šigelom uključuju crijevne i izvancrijevne manifestacije. Hemolitični uremični sindrom i komplikacije koje zahvaćaju središnji živčani sustav spadaju među najčešće izvancrijevne manifestacije šigeloze. Neurološke manifestacije, osobito konvulzije i encefalopatija, nisu česte kod šigeloze u djece. Edem mozga čest je nalaz u bolesnika s teškom encefalopatijom uzrokovanom šigelom. Proizvodnja toksina Shiga nije bitna za razvoj neuroloških simptoma udruženih sa šigelom. Ranim prepoznavanjem i ispravnim liječenjem teških slučajeva encefalopatije uzrokovane šigelom može se poboljšati njihov ishod. Prikazuje se slučaj 2,5-godišnje djevojčice s fulminantnom encefalopatijom uzrokovanom šigelom (sindrom Ekiri), kod koje je postignut potpun oporavak. Opisuju se nalazi kompjutorizirane tomografije ove bolesnice.

Deskriptori: KONVULZIJE; EDEM MOZGA; SINDROM; DISENTERIJA, BAKTERIJSKA; DIJETE, PREDŠKOLSKO

Primljeno/Received: 4. 7. 2011.
Prihvaćeno/Accepted: 16. 1. 2012.