Brief Communication

Shigella flexneri encephalopathy in a male child

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We associate shigellosis with fever, painful cramps in the abdomen and frequent loose stools with mucus, pus, or blood, and occasional neurological manifestations, including convulsions, encephalopathy or both. They usually occur before the appearance of diarrhea. The disease caused by *Shigella flexneri* is usually benign, and there are only few reports of associated fatal encephalopathy from industrialized or developing countries. During the 1980s and 1990s, there were 3 cases in children with *Shigella flexneri* associated fatal encephalopathy in South Africa,[1] one in Qatar,[2] 8 in Israel,[3] and one each in France[4] and the Netherlands.[5] Among 41 hospitalized Shigellosis children with seizures in Bangladesh, there were 12 fatal episodes.[6] We report a fatal case of *Shigella flexneri* encephalopathy in a 3-year-old male child domiciled in the Indian capital metropolis.

During December 2003, a 3-year-old male child, living in the western part of New Delhi, the Indian Capital metropolis, reported to the Sant Parmanand Hospital. The 140-bedded, tertiary care hospital caters for patients from the Capital and adjoining townships. The patient was the second child of a low middle-income Hindu family. He was not attending any boarding school, and was not malnourished. He had high-grade fever 12 hours before admission and loose stools without any blood for the last 6-8 hours. The patient had had 2 episodes of generalized tonic, clonic seizures (GTC). At the time of admission, he was conscious, cooperative, and temperature 38.9°C, pulse rate of 160 beats/minute but without any distress. There were signs of moderate dehydration. He did not show any meningeal signs, and there were no focal findings. The deep tendon reflexes were normal, and a Babinski sign was absent. There was a history of febrile seizure 6 months earlier. The total leukocyte count was 4.5×10^9/L, and the peripheral blood smear examination did not point to an infective etiology. The whole blood erythrocyte sedimentation rate was 15 mm for the first hour (Westergren), hemoglobin 145G/L; platelets count 302,000/cu^3 mm. The peripheral blood smear did not show any malaria parasite. The electrolytes were sodium 135.4 mmol/L, potassium 3.87 mmol/L and ionized calcium 1.16 mmol/L. The serum aspartate transaminase was 39 Units/L, blood urea was 80 mgm%, and creatinine level was 1.39 mgm%. Lumbar puncture was not performed. The stools showed 6-8 erythrocytes and 30-35 pus cells per high-powered microscopic field in the stools. The patient received rectal diazepam, antipyretics, correction fluids, and intravenous ceftriaxone. One hour later, he had GTC seizures and received loading dose of phenytoin. Consequently, the child became comatose, grade 3. Cranial computerized axial tomography was normal. After 7 hours of admission, the patient manifested tachycardia with a pulse rate of 200 beats/minute and respiratory rate, 90 breaths/minute. He was shifted to the intensive care unit where he had respiratory arrest. He was revived and put on mechanical ventilator. The peripheries were cold and comatose; the blood pressure was not measurable with a temperature of 38.9°C. Inotropic dobutamine was started to maintain blood pressure. Impending septicemia was addressed by amikacin and immunoglobulin. The child did not regain consciousness. Arterial blood gas analysis showed metabolic acidosis, which was ratified. Forty-eight hours after hospitalization, electroencephalography showed few spikes. The brain stem reflexes were negative including a negative brain stem evoked response audiography. The child continued on life support measures for another 24 hours before being declared dead. The family did not agree to a post-mortem examination. A post-mortem lumbar puncture, within 15 minutes after death, did not reveal any cells while Gram staining did not show any bacteria. Any meningitis was ruled out by CSF chemistry of proteins 60 mgm/dL and glucose, 50mgm/dL.

Bacteriological characterizations were accomplished in the Hospital and at the National Institute of Communicable Diseases, Delhi. Blood culture, using Bactec 9050, did not yield any growth after 3 days incubation. Identical culture of stools sample on MacConkey agar, Salmonella-Shigella agar, XLD agar (Difco) and desoxycholate citrate agar produced one type of non-lactose fermenting colonies. The isolate fermented glucose without gas, but did not ferment lactose or hydrolyze urea. There was no deamination of phenylalanine to phenylpyruvic acid, with no utilization of Simon citrated agar. Inoculation of triple sugar iron agar slopes produced an alkaline slant and acidic butt, without any gas or H_2S production. There was no gas including H_2S in lysine iron agar too. Slide agglutination using Shigella typing antiserum (Difco Laboratories, Michigan) was identified as positive for *Shigella flexneri* type 2. The isolate *Shigella flexneri* type 2 was sensitive to ceftriaxone, ciprofloxacin, ampicillin, gentamicin, amikacin, cephalexin, and chloramphenicol. The

isolate was resistant to tetracycline, nalidixic acid, and trimethoprim-sulfamethoxazole. The patient was prescribed the antibiotics that were found to be sensitive to *Shigella flexneri* during its *in-vitro* sensitivity assays. The *Shigella flexneri* type 2 isolate did not involve any other family member including a sibling and others housed in his neighborhood. The family consumed the water supplied by the local municipal authority.

Episodes of *Shigella flexneri* associated encephalopathy are not common, and are associated with a fatal outcome in children.[1,2] *Shigella flexneri* was incriminated in a vast majority of hospitalized cases with seizures accompanied by a sizable mortality in a *Shigella* endemic country, Bangladesh.[6] That indeed was exemplified in the above patient with shigellosis-associated mortality. Upon his admission, there were no meningeal signs or any focal findings. The normal deep reflexes and the negative Babinski sign were associated with seizures. Subsequently, after the fourth seizure, he had altered sensorium. We made a presumptive diagnosis of Shigella encephalopathy based on neurological findings, the finding of numerous pus cells and erythrocytes in stools as well as the results of electroencephalography. Pending stool and blood culture, we prescribed corrective fluids and antibiotics. We addressed further clinical deterioration by mechanical ventilator support and inotropes.

Contrary to an otherwise poor prognosis in episodes of *Shigella flexneri* encephalopathy, there is one recent instance of recovery in one 3-year-old child. The child with convulsions and fever at Soroka University Medical Center, Beer-Sheva, Israel developed severe septic shock and severe encephalopathy during an episode of *Shigella flexneri* dysentery. Mechanical ventilation, anticonvulsive and inotropic drugs, gentamicin, ceftriaxone, and intravenous fluids were effective in improvement of the general condition. The child not only regained alertness and consciousness but also became afebrile.[3]

We remain to elucidate the role of Shiga toxin, host factors, and bacterial traits in the pathogenesis of fatal *Shigella flexneri* associated encephalopathy. We cannot link the neurological manifestations of patients with shigellosis exclusively to the main toxic product of *S. dysenteriae*, the Shiga toxin. Among 15 fatal episodes of lethal encephalopathy in Israel, *S. dysenteriae* was isolated only from one patient.[3] The encephalopathy associated *Shigella flexneri* and *S. sonnei* isolates do not usually produce Shiga toxin. Moreover, both of them lack the structural genes encoding its production. A distinct cytotoxic activity with no similarity with Shiga toxin was demonstrated in stools from 5 patients with seizures or encephalopathy.[7] In Bangladesh, the majority of hospitalized patients with altered consciousness were not related to Shiga toxin.[6]

The contribution by host factors responsible for different clinical spectrum in shigellosis awaits in-depth investigation. Among children less than 5 years of age, behavioral and environmental factors contribute towards a higher or lower duration of illness with *Shigella dysenteriae* and *Shigella flexneri* associated infection.[8] In C3H/HeJ mice, Shiga toxin and lipopolysaccharide (LPS) enhance the animal sensitivity to pentylenetetrazole (PTZ)-induced seizures. The *in-vivo* response mediates through tumor necrosis factor alpha (TNF-α), interleukin-1-β, and nitric oxide. Shigella lethality and Shigella related seizures are linked with LPS and TNF-α.[9] Moreover, Shigellae with several distinct immunological and closely related types are associated with enteric disorders in humans and macaques. *Shigella flexneri* is responsible for diarrhea and symptomless bacterial excretion in rhesus monkeys in captivity. In several countries in Asia, humans and macaques share urban dwellings. We have yet to accomplish precise Shigella strain characterization by phage typing, plasmid, and chromosomal DNA analysis.

In conclusion, different pathological specimens including bacterial isolates from humans and macaques with symptomless excretion or with *Shigella* encephalopathy should be archived at the international reference centres. All specimens might be investigated to define components linked with episodes of otherwise poor prognosis Shigella encephalopathy. Such details would also simplify the standardization of even point-of-care techniques for rapid and sensitive diagnosis of Shigella encephalopathy. Certainly, an earlier point-of-care indication about encephalopathy would ensure prompt therapeutic intervention with anticonvulsive drugs, inotropic drugs, antibiotics, intravenous fluids, and mechanical ventilator.[10] Clinicians who are responsible for management of fulminate, near-fatal patients with shigellosis including encephalopathy[1-6] would find future point-of-care diagnostic an important in their clinical practice. Specimens from odd Shigella encephalopathy patients would merit investigations to define components linked with near fatality. Consequently, one may anticipate point-of-care diagnostics for odd instances of near fatal shigella encephalopathy. Clinicians responsible for near fatal cases would welcome such an armament for a recovery from those episodes.[4]

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