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Keratitis Due to *Shigella flexneri*

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Multiresistant *Shigella flexneri* isolates were cultured from the cornea and stool of a girl. Genetic analysis showed the isolates were identical. *Shigella* spp. are rare causes of ulcerative keratitis; there have only been 14 published cases since 1943. Although prognosis after local treatment is good, shigellosis is a systemic infection, possibly leading to dehydration.

**CASE REPORT**

An 8-year-old girl, whose father was born in Ghana, presented to the emergency department with a 5-day history of a painful red left eye and severe photophobia after her cornea was damaged by a fingernail of a girl in Ghana 5 days before. The patient had been otherwise well, except for a 2-day episode of slight diarrhea during her stay in Ghana. No additional information about the girl who caused the trauma was available. Physical examination disclosed a deep stromal tear with two infiltrates in the central part of the left cornea as well as a hypopyon. The conjunctiva was markedly injected. Visual acuity of the eye was limited to light perception. The iris, lens, and fundus were normal, and the pupil reaction was intact. The right eye was normal in every aspect. The girl had no fever, and the remainder of the physical examination was unremarkable. After admission to the hospital, corneal scrapings were obtained for culture, and empirical topical therapy using cefazolin (3.3%) and gentamicin (2.25%) eye drops every hour was started. *Shigella flexneri* was obtained in pure culture from the corneal scrapings. The isolate was susceptible to cefazolin, gentamicin, nalidixic acid, and ciprofloxacin; intermediate susceptibility to chloramphenicol; and resistant to amoxicillin, tetracycline, and trimethoprim-sulfamethoxazole. After the results of the culture were known, a fresh specimen of the stool was cultured from the stool, but cultures from the fingers were negative. Pulsed-field gel electrophoresis (PFGE) was performed according to the protocol described by McEllistrem et al. (21) using NotI digests (16). In short, the bacterial culture was suspended in 300 μl cell S-buffer (1 M NaCl, 10 mM Tris-HCl) and incubated with 5 U lyticase for 30 min at 37°C. Low-melting-point agarose was added, and the plugs were lysed in 4 ml lysis buffer (1 M NaCl, 100 mM EDTA, 6 mM Tris-HCl, 0.5% N-lauroyl sarcosine) supplemented with 1 mg of lysozyme/ml and 50 μg of RNase A/ml for 3 h at 37°C. Each plug was incubated with 5 U of Nlauroyl sarcosine and 100 μg of proteinase K/ml overnight at 50°C, and the plugs were washed and incubated overnight with NotI at 37°C. The plugs were loaded into a 1% agarose gel, and PFGE was performed with the contour-clamped homogeneous electric field mapping system in 0.5× Tris-borate-EDTA running buffer at the following parameters: pulse times of 3 to 30 s for 24 h with 200 V at 14°C. After electrophoresis, the gel was stained with ethidium bromide. PFGE patterns showed that the isolates from the cornea and the stool had the same genotype and that each of the seven unrelated *S. flexneri* isolates had a different genotype (Fig. 1). Based on the susceptibility pattern, therapy with gentamicin was continued for 14 days. Dexamethasone eye drops were prescribed for 2 months in a tapering low dose as soon as the susceptibility pattern was known to support corneal recovery. No systemic antimicrobial treatment was given.

The hypopyon vanished in 4 days. The corneal infiltrates diminished slowly. The keratitis resulted in slight corneal scarring. However, after 5 months the visual acuity had recovered to 20/25 (“Snellen” acuity) without correction.

Shigellosis, a gastrointestinal infection limited to humans, can occur at any age, but 69% of all episodes occurred in children under 5 years of age (14), presumably because of a lack of immunity and common fecal-oral transfer at that age. The age range of published cases of *Shigella* keratitis (from 3 months to 8 years) is in accordance with this high incidence of shigellosis in children (1–3, 5, 6, 9, 12, 13, 15, 17, 19, 20, 22). Little is known about the incidence of this complication in adults: corneal ulceration in a patient with dysentery (*Shigella* species unknown) during World War I was noted, although the association was not clear (22). It is possible that more hygienic behavior (better handwashing after defeation and/or less hand-eye contact) or the lower incidence of *Shigella* in adults diminishes the risk of contamination of the eye in that age group. Other ocular manifestations of shigellosis include conjunctivitis (during or after the acute infection) and iridocyclitis (20). Conjunctivitis can be associated with either urethritis or arthritis after the acute infection has subsided.

*Shigella* is a rare cause of infection of the cornea: no *Shigella* was cultured from 494 culture-proven corneal ulcers in New York (1950 to 1979) and from 238 such ulcers in Florida (1969 to 1977) (1) or identified among 1,558 isolates (from 1,303
patients) in Hyderabad, India (1991 to 1997) (15), although Shigella is a common cause of diarrhea in the latter country. One Shigella sonnei isolate was identified among 517 strains, cultured from patients with keratitis in Pittsburgh, Pa. (1993 to 1996) (9). However the number of children included was not mentioned in these publications. In contrast, two Shigella spp. were cultured from 50 children with ulcerative keratitis who were less than 16 years of age in Miami, Fla. (7). We found only 13 other cases in the literature since 1943. Eight out of 11 reports were written by American authors, which might indicate a publication bias. Surprisingly we did not find case reports from African, Asian, or South or Latin American countries.

In nearly all patients (10/12), diarrhea was mentioned (4 at the time of keratitis and in 5 preceding the keratitis by 2 to 10 days). Shigella spp. were isolated from the stool from 10/14 patients, suggesting the stool as a source of autoinoculation. The infection was unilateral in all patients. Bloodborne infection seems less likely, because there are no blood vessels in the healthy cornea and bloodstream dissemination of Shigella spp. is rare (3). In accordance with this, no Shigella was cultured from the blood of four patients with keratitis, whose blood was cultured (4, 11, 25, 27).

S. sonnei was isolated as frequently (4/8) as S. flexneri, which might reflect the predominant species in the involved countries during that time (S. sonnei replaced S. flexneri as the predominant species in the industrialized countries after World War II) (13). In one patient, both S. sonnei and Staphylococcus aureus were isolated from the cornea from two separate cultures. Little is known about the association between keratitis and, respectively, Shigella dysenteriae and Shigella boydii. These species are both less frequent (together 3% in industrialized and 12% in developing countries) (14), although S. dysenteriae was the predominant species in the world until World War I, and this species has been documented as a reemerging pathogen in Latin America, central Africa, Asia, and the Indian subcontinent since the 1970s (12). It has been mentioned that keratoconjunctivitis associated with S. dysenteriae has been reported in the past (18), and keratitis in a case of dysentery (variety not stated) had been briefly reported in 1913 (5).

The recovery of the same genotype of S. flexneri from the cornea and the stool of our patient suggests autoinoculation of the damaged cornea via the fingers, after the trauma had happened, although another possibility is that the same species was present under the nails of the other girl as well and contaminated the cornea of the patient at the time of the trauma in Ghana. No microbiological data for the latter were available, and the incubation period (1 to 7 days, usually 1 to 3 days) did not discriminate between these two possibilities. The isolate was resistant to amoxicillin, tetracycline, and trimethoprim-sulfamethoxazole. This multiresistance has appeared in most areas of the world, but is more common in African and Asian than in industrialized countries and is probably related to widespread use of antibiotic agents.

A great number of organisms may cause keratitis if there is a corneal defect, but only a limited number, including Shigella spp., Neisseria gonorrhoeae, and Corynebacterium diphtheriae, have the ability to penetrate an intact cornea by the release of toxins or enzymes: unlike with our patient, the cornea in 7 out of 12 published cases was intact (Table 1). So, although the damage to the cornea of our patient could have facilitated the entry of the microorganisms, it was possibly not essential for the emergence of the infection. Virulent strains of Shigella spp. can, in contrast to, for example, Salmonella and other gram-negative species, penetrate the intact cornea of rabbits and guinea pigs. In rabbits, the cornea became necrotic and opaque about 5 days later, but corneal transparency was regained spontaneously without scar formation within 3 weeks after inoculation (6). In the cornea of contaminated guinea pigs, ulceration was noted by the third day. Unless the infection became chronic, which might last for 6 months or longer, healing was completed without treatment within 3 weeks to 6 months with slight residual scarring (19). Recovered eyes of rabbits and guinea pigs were immune to reinfection.

In most of the published patients, only minor scars remained (7/11) or even full resolution (2/11) was observed; but in 2 patients there was still heavy scarring 4 months later or a diffusely cloudy cornea on day 30 (Table 1).

Topical antimicrobial therapy is indicated in bacterial keratitis, because of the dangers of perforation and visual loss due to central scarring. As long as the organism and the results of the susceptibility testing are not yet known, a broad-spectrum antibiotic regimen, including gentamicin or one of the fluoroquinolones, like ofloxacin, is indicated, because it is unlikely that even multiresistant Shigella spp. are resistant to these drugs. Cycloplegics are indicated if there is a severe anterior chamber reaction to relieve ciliar spasm and prevent the formation of synchiae. Mydriatics were given to 8 of 12 patients. It is not clear if the use of topical corticosteroids to minimize the inflammatory sequelae can adversely affect the results of the antimicrobial therapy. Experiments in animals with Staphylococcus aureus and Pseudomonas aeruginosa suggest that ste-
TABLE 1. Clinical data and outcome of keratitis by *Shigella* spp.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Preceding event/defect</th>
<th>Cornea presentation</th>
<th>Culture</th>
<th>Source</th>
<th>Systemic signs</th>
<th>Effective treatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>9 mo</td>
<td>No</td>
<td>Small ulcer (right) just below center of pupil, anterior uveitis</td>
<td><em>S. sonnei</em></td>
<td>Eye, stool</td>
<td>Dysentery, fever</td>
<td>Sulfonamide orally, atropine</td>
<td>Very small scar, restored pupil reaction after 50 days</td>
<td>26</td>
</tr>
<tr>
<td>Male</td>
<td>6 yr</td>
<td>Trauma (pair of scissors) 7 days before</td>
<td>Ulcer (right), lower one-half</td>
<td><em>S. flexneri</em></td>
<td>Eye</td>
<td>Diarrhea</td>
<td>Chloramphenicol, neomycin, polymyxin B, gramicidin, atropine</td>
<td>Heavy scar formation (4 mo)</td>
<td>18</td>
</tr>
<tr>
<td>Male</td>
<td>2 yr</td>
<td>No Ulcer (left) with large opacity</td>
<td><em>S. flexneri</em></td>
<td>Eye, stool</td>
<td>Diarrhea, fever, moderate dehydration</td>
<td>Rehydration, oral gentamicin, neomycin, polymyxin B, sulfonamide (also orally), steroids initially*</td>
<td>Corneal diffuse cloudy appearance (day 30)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 yr</td>
<td>Blunt trauma 5 days before</td>
<td>Ulcer (right), anterior uveitis</td>
<td><em>S. sonnei</em> and <em>S. aureus</em></td>
<td>Eye</td>
<td>Fever (38.1°C)</td>
<td>Neomycin, polymyxin B, sulfonamide, phenylephrine/scopolamine</td>
<td>Residual paracentral nebu</td>
<td>10</td>
</tr>
<tr>
<td>Male</td>
<td>2 yr</td>
<td>Herpes keratitis? Large ulcer (left) involving lower third</td>
<td><em>S. sonnei</em></td>
<td>Eye, stool</td>
<td>Diarrhea until 3 days before onset</td>
<td>Gentamicin, neomycin, polymyxin B, gramicidin, oral cephalaxin, debridement</td>
<td>Faint stromal scar, vision 6/9 (6 wk)</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 yr</td>
<td>No Ulcer (left), lower one-half, mild anterior uveitis</td>
<td><em>S. flexneri</em></td>
<td>Eye, stool</td>
<td>Diarrhea, fever, and seizures 10 days before</td>
<td>Gentamicin, chloramphenicol, atropine</td>
<td>Superficial scar (4 mo)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2 yr</td>
<td>No Several ulcers (left)</td>
<td><em>S. sonnei</em></td>
<td>Eye, stool</td>
<td>Diarrhea 10 days before</td>
<td>Gentamicin (also parenteral), atropine</td>
<td>Full resolution</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1 yr</td>
<td>No 3 ulcerations (left)</td>
<td><em>S. sonnei</em></td>
<td>Eye</td>
<td>Diarrhea 4-6 days before</td>
<td>Cefazolin, gentamicin, homatropine</td>
<td>Small peripheral scars (day 20)</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1 yr</td>
<td>Red eyes last week before</td>
<td>Large ulcer (right) inferior lateral, 2 ulcers superior medial</td>
<td><em>S. sonnei</em></td>
<td>Eye</td>
<td>No diarrhea</td>
<td>Cefazolin, gentamicin, atropine</td>
<td>Minimal scar (day 26)</td>
<td>27</td>
</tr>
<tr>
<td>Female</td>
<td>3 mo</td>
<td>No Ulcer (1 by 2 mm) (left) hypopyon</td>
<td><em>S. flexneri</em></td>
<td>Eye, stool</td>
<td>Diarrhea, fever, severely dehydrated</td>
<td>Gentamicin, chloramphenicol, ampicillin i.v.</td>
<td>Died (day 6)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 yr</td>
<td>Herpes keratitis</td>
<td><em>S. sonnei</em></td>
<td>Eye, stool</td>
<td>Diarrhea until 2 days before</td>
<td>Tobramycin, cefazolin (1%), atropine</td>
<td>Recovered</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8 yr</td>
<td>Nail Trauma by fingernail (left), 2 central ulcers, hypopyon</td>
<td><em>S. flexneri</em></td>
<td>Eye, stool</td>
<td>Diarrhea recently</td>
<td>Cefazolin, gentamicin, steroids</td>
<td>Hypopyon vanished in 4 days, slight scarring; visual acuity 20/25 (5 mo)</td>
<td>Present case</td>
<td></td>
</tr>
</tbody>
</table>

*a* Antimicrobial agents associated with clinical improvement or in vitro susceptibility; local therapy unless stated otherwise. i.v., intravenous.

*b* Associated with progression.

Died in combination with bactericidal antibiotics do not have this effect (2). Whether the early addition of corticosteroids to the antibiotic treatment has contributed to the favorable outcome of the patient is unknown.

It is important that the ophthalmologist realize that shigellosis can be a serious systemic disease, especially in the very young; 2 out of 14 patients with keratitis were dehydrated (respectively, 2 years and 3 months old), and the 3-month-old girl died. If *Shigella* is isolated from the eye, culture of the stool is indicated. Antimicrobial treatment was restricted to the eye in 7 out of 12 patients, including our patient. In five patients, antimicrobial agents active outside the eye were also prescribed to treat the systemic infection (four patients) or to treat the gastroenteritis locally (one patient). Although shigellosis is normally self-limited, lasting an average of 4 to 7 days, and carriage usually ceases within 4 weeks, systemic antimicrobial therapy is indicated in all cases, including mild, nondysenteric infections, to prevent spread of the organism (8). A short course (3 to 5 days) of systemic antibiotics, to which the organism is susceptible, will cure the infection and interrupt fecal excretion. It has even been advised to treat carriers, because person-to-person transmission is common (8).

The large-scale use of antibiotics has led to considerable resistance of *shigellae* to ampicillin and tetracycline and in developing countries (including Africa, south-east Asia, and South America) to trimethoprim-sulfamethoxazole as well. A
fluoroquinolone is suitable for empirical systemic treatment, because resistance is rare, although routine use of fluoroquinolones in children is not approved. The combination of trimethoprim with sulfamethoxazole (co-trimoxazole) is considered a second-best choice. Infection prevention precautions ("enteric precautions"), with strict attention to hand disinfection, are indicated if the patient is admitted to the hospital, because the organism is easily transmitted, and these precautions are advised until three stool cultures after cessation of antimicrobial therapy are negative.

REFERENCES