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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 susceptible to chloramphenicol; and resistant to amoxicillin, tetracycline, and trimethoprim-sulfamethoxazole. After the results of the culture were known, a fresh specimen of the stool and a swab from the last digit of each finger were cultured: *S. flexneri* with the same susceptibility pattern was isolated 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 digestions (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 4 ml of ES buffer (0.5 M EDTA, 1% *N*-lauroyl 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 defecation and/or less hand-eye contact) or the lower incidence of *Shigellosis* 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

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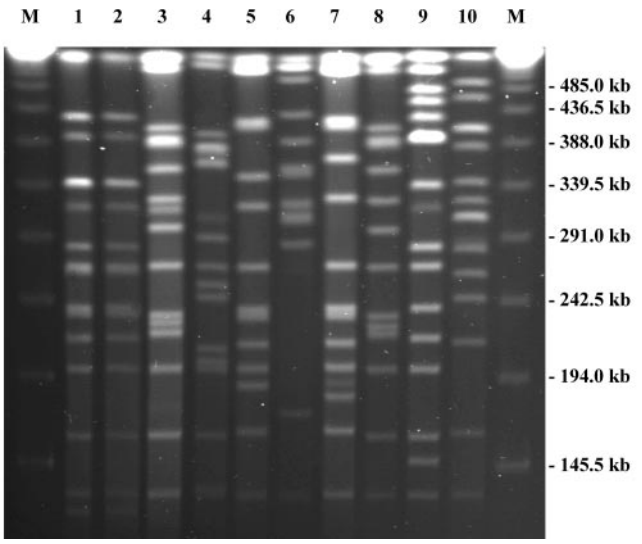

FIG. 1. Molecular typing of *Shigella flexneri*. An agarose gel shows the NotI digestion patterns of *Shigella flexneri* isolates from the patient's cornea (lane 1) and stool (lane 2) and unrelated *S. flexneri* strains (lanes 4 to 10) included as controls. Lanes 4 to 7 represent different clinical *S. flexneri* isolates, and lanes 8 to 10 represent different *S. flexneri* strains included in the distributed Dutch quality proficiency panel. M indicates the marker lanes. The sizes of marker bands are shown on the right.

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 bloodborne 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 diphtheria*, 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 synechae. Mydriatics were given to 8 of 12 patients.

It is not clear if the use of topical corticosteroids to minimize the inflammatory sequellae 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.

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

[a] Antimicrobial agents associated with clinical improvement or in vitro susceptibility; local therapy unless stated otherwise. i.v., intravenous.
[b] Associated with progression.

roids 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.

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