

***Shigella flexneri* ve *Shigella sonnei*'nin Neden Olduğu İki Vulvovajinit Olgusu: Olgu**

Sunumu

Anahtar sözcükler: *Shigella flexneri*, *Shigella sonnei*, vulvovajinit, prepubertal kız çocukları.

Two Cases of Vulvovaginitis Caused by *Shigella flexneri* and *Shigella sonnei*: A Case report

Key words: *Shigella flexneri*, *Shigella sonnei*, vulvovaginitis, prepubertal girls.

ÖZET

Shigella species (Shigella spp.)'in neden olduğu vulvovajinitler nadir olarak bildirilmiştir. Burada kanlı irinli vaginal akıntı şikayeti ile başvuran ve birinde ampisilin dirençli *Shigella flexneri* ve diğerinde trimetoprim-sulfametoksazole dirençli *Shigella sonnei* tespit edilen prepubertal vulvovajinitli iki olgu sunulmaktadır. Bulgularımız kuvvetle düşündürmektedir ki özellikle bu patojenlerin endemik olduğu gelişmekte olan ülkelerde vulvovajiniti olan prepubertal kız çocuklarında *Shigella spp.*'nin tanımlanması ve antibiyotik duyarlılık testi göz ardı edilmemelidir.

ABSTRACT

Vulvovaginitis caused by *Shigella species (Shigella spp.)* has been rarely reported. This paper describes two cases of prepubertal vulvovaginitis, presenting with a bloody and purulent vaginal discharge, separately caused by ampicillin-resistant *Shigella flexneri* and trimethoprim-sulfomethoxazole-resistant *Shigella sonnei*. Our conclusions are following: *Shigella spp.* are the potential cause of vulvovaginitis in prepubertal girls in developing countries where these pathogens are endemic, and identification of the bacteria and making antibiotic susceptibility testing in these cases should not be overlooked.

INTRODUCTION

Shigellosis or bacillary dysentery is a global human health problem with an estimated annual incidence of 164.7 million cases, of which 163.2 million occur in developing countries, and causes 1.1 million deaths.^[1] *Shigella* species are not the part of the normal human flora, and well-recognized agents of acute bacillary dysentery.^[2] Vulvovaginitis caused by *Shigella spp.* have

29 been rarely reported.^[3-9] This may be partly due to the fact that diagnosis of *Shigella*
30 vulvovaginitis may be difficult. Most of these cases are reported in children.^[3-9]

31 We describe here two cases of vulvovaginitis caused by *Shigella flexneri* and *Shigella*
32 *sonnei*, and discuss some problems of the diagnosis and treatment of vulvovaginitis caused by
33 *Shigella* spp.

34 CASE REPORTS

35 Case 1

36 A nine-year-old girl was referred to our department for further evaluation of dyslipidemia and
37 purulent vaginal discharge of unknown etiology. She had a history of bloody-purulent vaginal
38 discharge, and vulvovaginal itching for two months. There were no findings for any sexual abuse,
39 history of serious illness and hospitalization, and the presence of any foreign body.

40 Vulvovaginal examination showed mucosal erythema with a yellowish purulent vaginal
41 discharge mixed with blood. Gram stain smear of the vaginal discharge showed numerous
42 polymorphonuclear leucocytes, gram-negative bacilli and predominant growth of *Escherichia*
43 *coli*. No intracellular gram-negative diplococci were seen at microscopic examination. The urine
44 culture was negative. Based on the diagnosis of nonspecific vaginitis, the patient was advised for
45 local hygienic measures. Since *E. coli* growth might have been due to the contamination from the
46 perianal skin, vaginal culture was repeated five days later and *S. flexneri* was identified. The third
47 vaginal culture was again positive for *S. flexneri*. The patient's and other family members' stool
48 cultures were negative for *S. flexneri*. The *S. flexneri* isolate was susceptible to ceftriaxone,
49 ceftazidime, cefepime, ciprofloxacin, levofloxacin, chloramphenicol, trimethoprim-
50 sulfamethoxazole, imipenem, meropenem and tigecycline and resistant to ampicillin and
51 amoxicillin-clavulanic acid. The patient was treated with oral trimethoprim-sulfamethoxazole for
52 10 days, and follow-up vaginal cultures were found negative.

53 Case 2

54 An eight-year-old girl presented to our department with a one-year history of intermittent foul
55 smelling, yellowish purulent vaginal discharge and severe vulvovaginal itching. The discharge
56 had turned bloody in last two months. Although treated elsewhere with unknown oral medication

57 for one year, her symptoms had not improved. No other health problem, any sexual abuse and
58 trauma was reported.

59 The physical examination at admission showed a reddish vaginal mucosa and bloody-
60 vaginal discharge. No vaginal foreign body was detected. *S. sonnei* resistant *in vitro* to
61 trimethoprim-sulfamethoxazole but susceptible to ampicillin, amoxicillin-clavulanic acid,
62 ceftriaxone, ceftazidime, cefepime, ciprofloxacin, levofloxacin, chloramphenicol, imipenem,
63 meropenem and tigecycline grew in the vaginal culture. The Gram-stained smear of the vaginal
64 discharge showed numerous polymorphonuclear leucocytes but no gram-negative diplococci.
65 Patient and family members' stool cultures were negative for *Shigella* spp. and any other enteric
66 pathogens. She was treated orally with amoxicillin-clavulanic acid for 10 days. The vaginal
67 discharge was not resolved after 10 days of the treatment. On the third day after completion of
68 antibiotic therapy, *S. sonnei* at 100 cfu per milliliter with the same susceptibility pattern was
69 isolated from urine, but the repeated cultures from the vaginal discharge were negative. No
70 further culture was performed since the patient made no further visits to our clinic for a month.
71 When she returned after one month, vaginal culture had remained positive, and stool and urine
72 cultures were negative for *S. sonnei*. The patient was prescribed oral cefixime for 10 days, and at
73 follow-up examination, vaginal culture was positive for *S. sonnei*. The patient was given a 14-day
74 course of ciprofloxacin. The vaginal discharge resolved after the treatment with ciprofloxacin.
75 Follow-up vaginal cultures were negative.

76 DISCUSSION

77 Chronic vaginal discharge is the most frequent finding in *Shigella* vulvovaginitis and, as also
78 noted with our cases, is resolved in longer than 10 days. The purulent-mucopurulent foul smelling
79 discharge, varying from whitish to yellowish to greenish, does not differ from vulvovaginitis
80 caused by the other microorganisms, however, the bloody discharge could be a clue for *Shigella*
81 vulvovaginitis.^{15,9} As shown in table 1, eight out of 11 cases (73%), including ours, presented
82 with bloody-vaginal discharge. Here no significant difference between *S. flexneri* and *S. sonnei*
83 infection regarding to the frequency of bloody discharge has been detected, although bloody
84 diarrhea due to *S. flexneri* has been reported more often compared to that of *S. sonnei*.¹⁹

85 Laboratory diagnosis of *Shigella* vaginal infections is not easy. One of the possible
86 reasons is that a request for the identification of *Shigella* is not common since many microbiology

87 laboratories may not identify gram-negative rods recovered from vaginal cultures.^[4,7] For
88 instance to isolate and differentiate *Shigella* spp. in samples containing bacterial flora, it is
89 advised that clinical sample should be inoculated onto Salmonella Shigella (SS) agar, eosin-
90 methylene blue (EMB) and selenite broth (SB) and incubated for longer times.^[10] None of these
91 growth media are mentioned among the media suggested for routine culturing of vaginal samples.
92 When it has been done, the suggested media for vaginal specimens of children are 5% sheep
93 blood agar and chocolate agar for *Streptococcus pyogenes*, *Streptococcus pneumoniae* and
94 *Haemophilus influenzae*, Sabouraud medium for *Candida* spp. and selective gonococcal medium
95 for *Neisseria gonorrhoeae*. Because, *Shigella* spp. and other gram-negative bacilli are not
96 considered as possible vulvovaginitis pathogens in prepubertal girl,^[11] and gram-negative rods
97 (such as *Proteus* species, *Pseudomonas* species) known to occur in healthy prepubertal girls
98 without causing any illness.^[12] Additionally, Gram-negative rods of fecal origin can also be found
99 as contaminants. As a result, *Shigella* spp. is easily overlooked in routine vaginal cultures if no
100 pure or prominent growth was detected. Another reason for missing *Shigella* in laboratory
101 diagnosis is inaccurate specimen collection and transportation. *Shigella* spp. are fragile organisms
102 and remain viable for a limited time outside the human body. Therefore, considerable care must
103 be taken in collection and transportation of the clinical specimens, and informing the laboratory
104 about the possible causative agents.^[13] For a fast and accurate diagnosis, the microbiology
105 laboratory should be certainly informed by clinicians if a *Shigella* infection is considered or if
106 vaginal discharge with blood is present in the patient. The presence of leucocytes in vaginal
107 secretions may be an indicator for clinicians.

108 Because of the infrequency of the disease, and the limitations in clinical experience, the
109 optimal therapy for *Shigella* vulvovaginitis remains uncertain.^[7,8] Systemic antibiotic therapy is
110 generally recommended as being more effective than topical antibiotic therapy.^[4,6,8] Although the
111 recommended standard course of therapy for shigellosis is oral ampicillin or trimethoprim-
112 sulfamethoxazole therapy, it should be noted that while initially susceptible, most *Shigella*
113 isolates are currently resistant to these antibiotics. These are inappropriate for empiric therapy
114 unless local microbiological data suggest susceptibility.^[1,6,8]

115 In the treatment of Shigellosis, intracellular concentrations of antibiotics are probably the
116 crucial determinants of the success, since *Shigella* spp. multiply intracellularly. Fluoroquinolones
117 such as ciprofloxacin, and macrolides such as azithromycin, may be particularly useful for the

118 treatment of shigellosis, because, they reach high intracellular levels.^[13,14] On the other hand, the
119 use of fluoroquinolone in children has been limited because of the concerns about its toxicity,
120 however, there is growing evidence of their safety for the treatment of shigellosis in children.^[1,12]
121 Azithromycin is approved for use in children.^[13,14] The significant disadvantage of the
122 azithromycin is the lack of Clinical Laboratory Standards Institute-defined breakpoints for it for
123 the *Enterobacteriaceae*, including *Shigella* spp.^[15] Susceptibility of the *Shigella* isolates to
124 azithromycin is not routinely tested in most countries which use Clinical Laboratory Standards
125 Institute documents for antibiotic susceptibility tests, including Turkey.

126 In our first case, the *S. flexneri* isolate was susceptible to a variety of agents including
127 trimethoprim-sulfamethoxazole, and the infection was successfully treated with oral
128 trimethoprim-sulfamethoxazole. In our second case, however, the *S. sonnei* isolate was
129 susceptible *in vitro* to amoxicillin/clavulanic acid and cefixime, but the treatments with these
130 antibiotics were not successful. A failure with amoxicillin/clavulanic acid and cefixime was also
131 reported by Baiulescu et al.^[6] in a child with *Shigella* vulvovaginitis, in which the organism was
132 susceptible *in vitro* to amoxicillin/clavulanic acid and cefixime, but the patient exhibited clinical
133 and microbiologic failure until ciprofloxacin therapy was instituted. Our case and the case
134 reported by Baiulescu et al.^[6] differ only in respect to the agents isolated, *S. sonnei* and *S.*
135 *flexneri*, respectively. The failures in treatment with amoxicillin/clavulanic acid and cefixime
136 suggest a possible difference in the form of infection rather than *Shigella* species. It is likely that
137 involvement of gynecological tissue complicates the success of the management.

138 In conclusion, our experience strongly suggests that identification and antibiotic
139 susceptibility testing for *Shigella* spp., as a potential cause of vulvovaginitis in prepubertal girls
140 presenting with chronic vaginal discharge, especially in developing countries where these
141 pathogens are endemic, should not be overlooked. Additionally, our current understanding
142 suggests that fluoroquinolone antibiotics such as ciprofloxacin might not be the first but
143 nevertheless the best choice against vulvovaginitis for the patients not responding to the regular
144 treatment, and there is not always a good correlation between *in vivo* clinical response and *in*
145 *vitro* antibiotic susceptibility test results.

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184 **Table 1.** Reported Cases (Including the Present Cases) of *Shigella* Vulvovaginitis. At the very left column, the number of the cases; at
 185 the top line, the features of the cases have been shown. Please note that last two cases are described here.

Case	Year	Ref.	Age	<i>Shigella</i> species	Bloody discharge	Associated symptoms	Antibiotic resistance pattern	Ineffective Treatment	Effective Treatment
1	1950	(3)	7	<i>S. flexneri</i>	No	No	ND	No	Sulphaguanidine orally
2	1975	(4)	6	<i>S. flexneri</i>	Yes	No	ND	No	Ampicillin orally
3	1975	(4)	4	<i>S. flexneri</i>	Yes	Urinary frequency and dysuria	ND	No	Ampicillin orally
4	1975	(4)	4	<i>S. flexneri</i>	Yes	Dysuria	ND	No	Ampicillin orally
5	1975	(4)	6	<i>S. flexneri</i>	Yes	No	ND	Nitrofurantoin, ampicillin orally	Estrogen/sulfasoxazole intravaginally
6	1979	(5)	4	<i>S. sonnei</i>	No	No	Ampicillin	Ampicillin orally	Estrogen/sulfasoxazole intravaginally
7	2002	(6)	7	<i>S. flexneri</i>	Yes	Dysuria	Ampicillin, SXT	SXT, AMC, cefixime orally	Ciprofloxacin orally
8	2002	(7)	5	<i>S. flexneri</i>	Yes	No	No resistance	No	SXT orally
9	2006	(8)	5	<i>S. flexneri</i>	No	Dysuria	Ampicillin, SXT	No	Cefixime orally
10*	2009		9	<i>S. flexneri</i>	Yes	No	Ampicillin, AMC	No	SXT orally
11*	2009		8	<i>S. sonnei</i>	Yes	No	SXT	AMC, cefixime orally	Ciprofloxacin orally

186 ND= Not described, SXT = Trimethoprim–sulfamethoxazole, AMC= Amoxicillin-clavulanic acid

