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CASE REPORT

Haemophilus parainfluenzae urethritis among homosexual men



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Haemophilus parainfluenzae is a common inhabitant of the human upper respiratory tract of the normal oral microflora. We report three men who had been having unprotected sex with men (MSM) and subsequently acquired *H. parainfluenzae* urethritis, which was confirmed by 16S rRNA gene sequencing analysis. Two men were treated with ceftriaxone and doxycycline, and the third man was treated with clarithromycin. All three patients responded to treatment. This case series highlights the potential role of *H. parainfluenzae* as a sexually transmitted genitourinary pathogen.

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Introduction

Haemophilus parainfluenzae is a common inhabitant of the human upper respiratory tract and a member of the normal oral microflora. Rare cases of male urethritis have been reported.^{1–4} In this paper, we report three cases of urethritis, caused by *H. parainfluenzae*, that were initially misidentified as *Pasteurella pneumotropicalis*.

Case reports

Case 1

A 29-year-old man (Patient 1) visited our urologic outpatient department with the presentation of dysuria and purulent urethral discharge, which he had had for several days. He denied other medical disease, but he had been having unprotected sex with a man preceding this episode. Physical examination only revealed urethral discharge. His discharge was swabbed for bacterial culture. Chocolate agar was used to screen for gonococcal infection. Urine analysis showed no pyuria. His serology was negative for human immunodeficiency virus (HIV) and syphilis. Under

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the impression of urethritis, he was prescribed an intramuscular injection of 250 mg ceftriaxone stat and 100 mg of oral doxycycline twice daily for 7 days.

Case 2 and Case 3

The following week, two young males—Patient 2 (Case 2), who was 32 years old, and Patient 3 (Case 3), who was 27 years old—also visited our outpatient department with the same complaint as Patient 1 (Table 1). Both of these patients had been having unprotected sex with men. Their physical examinations revealed a purulent urethral discharge. In Patient 3, one elastic and tender lymph node (1 cm) was also noted in the right inguinal area. Patient 2 was administered ceftriaxone and doxycycline, as described for Patient 1. Under the impression of lymphogranuloma venereum, Patient 3 was prescribed clarithromycin 500 mg twice daily (Table 1).

The samples from all three patients showed colonies after undergoing an overnight incubation on chocolate agar at 37°C in 5% CO₂. The colonies were smooth, 1–2 mm in diameter, gray, and flat to convex. Because of a negative oxidase reaction and the colonies' appearance, infection by *Pasteurella* was suspected; this was supported by biochemical reactions.⁵ We tested these isolates with the BD Phoenix Automated Microbiology System (Beckon Dickinson, Sparks, MD, USA), which identified the organism as *Pasteurella pneumotropicalis*. However, we further tested the isolates with 16S rRNA gene sequencing analysis. The primers 5'-AGAGTTTGATCTGGCTCAG-3' and 5'-GGTTACCTTGTTACGACTT-3' were used in accordance with a previous report. The result showed a high degree of sequence similarity with *H. parainfluenzae* (GenBank accession FJ939584.1, maximal identity 98–99%).⁶ An antimicrobial susceptibility test with a disc diffusion method was further performed. Direct colony suspension with an equivalent of 0.5 Mcfarland standard was inoculated on *Haemophilus* test medium (HTM) (Beckon Dickinson, BD). Ampicillin (10 µg), ceftriaxone (30 µg), ciprofloxacin (5 µg), doxycycline (30 µg), and clarithromycin (15 µg) were tested. The susceptibility result was described in accordance with the suggestion of the Clinical and Laboratory Standards Institute.⁷ The results showed that all three isolates were susceptible to ceftriaxone and clarithromycin, but that all were resistant to tetracycline.

We then used three biochemical reactions in the biotyping of *H. parainfluenzae*: indole production, urease activity, and ornithine decarboxylase activity.⁵ Two of the isolates were type II and one isolate was type III. Because of the short time frame (3 cases within 1 week), an outbreak was suspected. Pulse gel electrophoresis was performed for these isolates with the digestive enzyme Apal (CHEF Bacterial Genomic DNA Plug Kit and CHEF Mapper; Bio-Rad, Hercules, California). This procedure refuted a clonal outbreak. The lack of association was also supported by the different antimicrobial susceptibilities, as shown in Table 1.

The urine cultures of two patients showed the concomitant presence of *Enterococcus* species with *H. parainfluenzae*. One patient had *Morganella morganii* and *Neisseria gonorrhoeae* growing on the chocolate agar with *H. parainfluenzae*. All patients responded to empirical treatment.

Table 1 Characteristics of the three males with *Haemophilus parainfluenzae* urethritis

Patient No.	Age	Complaints	U/A	Urinary co-pathogen	Biotype	Drug sensitivity							Treatment	Outcome
						AM	CRO	CIP	SXT	TET	CL			
1	28	Dysuria	No pyuria	<i>Enterococcus</i> spp.	II	R	S	S	R	R	R	S	Ceftriaxone 250 mg IM and doxycycline (100 mg twice daily) × 7 days	Responded to treatment
2	32	Dysuria and frequency	No pyuria	<i>Neisseria gonorrhoeae</i> ; <i>Morganella morganii</i>	III	S	S	S	I	R	S	S	Ceftriaxone 250 mg IM and doxycycline (100 mg twice daily) × 7 days	Responded to treatment
3	27	Dysuria	NP	<i>Enterococcus</i> spp.	II	S	S	S	R	R	S	S	Clarithromycin (500 mg twice daily) × 7 days	Responded to treatment

AM = ampicillin; CIP = ciprofloxacin; CL = clarithromycin; CRO = ceftriaxone; I = intermediate susceptible; IM = intramuscular; NP = not performed; R = resistant; S = susceptible; SXT = trimethoprim-sulfamethoxazole; TET = tetracycline; U/A = urine analysis test.

Discussion

Haemophilus parainfluenzae is a pathogen of sexually transmitted source of urethritis in men. Fuzi first reported this in 1980. However, rare cases have been reported in the recent decade. Indistinctive clinical symptoms or signs in our three cases and in previous reports also make it difficult to differentiate *H. parainfluenzae* urethritis from other types of urethritis.^{1–4,8} Our three consecutive cases alert us the “forgotten” role of this pathogen in sexual transmitted disease. In 1987, Clairmont et al reported *H. parainfluenzae* prostatitis in a homosexual man with chronic lymphadenopathy syndrome and HIV infection.⁹ All three of our male patients had a history of sex with other males, but all had negative HIV enzyme-linked immunosorbent assay (ELISA) test results. Two of the *H. parainfluenzae* isolates were biotype II. Biotype III was isolated from one patient. Previous reports in the literature shows that biotype III *H. parainfluenzae* is mainly in the throat, whereas biotype II is more prevalent in the anogenital area.^{10,11} This biotyping may imply that both genital and/or orogenital contact are possible modes of transmission. Further study is necessary to clarify the association of this pathogen with sexual behavior.

The grayish colonies on the chocolate agar were initially misidentified as *Pasteurella pneumophila*; however, 16S RNA indicated that all three isolates were *H. parainfluenzae*. Misidentification between *Haemophilus aphrophilus* and *Pasteurella* spp. has previously been reported.^{12,13} This is the first report to specifically demonstrate the possibility of misidentification between *H. parainfluenzae* and *P. pneumotropicalis*. Because of the overlap and the exceptions to the phenotypic descriptions of *Pasteurella*, *Haemophilus*, and *Actinobacillus*, it is sometimes quite difficult to differentiate these genera.¹⁴ Therefore, we suggest that further 16S RNA confirmation is necessary in the event that *Pasteurella* species are isolated from an unexpected source (i.e., without suggested animal contact) and identified by an automated system. Pulsed field gel electrophoresis shows that the three isolates are not identical; however, the clustering of cases reminds us of the role of *H. parainfluenzae* as a pathogen of urethritis.

Most patients in previous reports of *H. parainfluenzae* urethritis were cured after 1 week (approximately 5–7 days) of oral amoxicillin (500 mg every 6–8 hours) or 1 week of oral doxycycline (100 mg twice daily).^{1–4} However, one isolate in this report was resistant to ampicillin (Patient 1) and all three isolates were resistant to doxycycline. This indicates these two agents may not be active against *H. parainfluenzae* urethritis in Taiwan. All patients responded to one shot of ceftriaxone (250 mg) by intramuscular injection or to oral clarithromycin (500 mg twice daily). We suggest that one intramuscular injection of ceftriaxone or 1 week of clarithromycin should substitute for doxycycline or ampicillin to treat *H. parainfluenzae* urethritis.

The greatest limitation of our report is that we could not exclude the possibility that *H. parainfluenzae* is a colonizer since there were concomitant bacteria. However, *H. parainfluenzae* was the dominant bacteria on the plate for all three patients. A study by Sturm showed that *H. parainfluenzae* could be isolated from 10% of men with urethritis and no *Haemophilus* is in asymptomatic men.² The reported

frequency of *Haemophilus* colonization in the male urethra ranges from 3% to 9.3%, depending on the culture method and the patient selection.^{1–5,15} Further prospective study is required to clarify the frequency of colonization.

In summary, we present three cases of *H. parainfluenzae* urethritis treated with ceftriaxone or clarithromycin. With the increase in sexually transmitted diseases and variable human sexual behaviors, the significance of *H. parainfluenzae* as a sexually transmitted pathogen should be considered. Laboratory workers should consider the possibility of isolating *H. parainfluenzae* on chocolate agar from urethral discharge specimens.

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