

Gonorrhoea in Rotterdam caused by penicillinase-producing gonococci

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SUMMARY Recently the prevalence of strains of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) in the Netherlands has increased. A study of demographic and clinical data from patients with gonorrhoea due to PPNG strains, and of the biological characteristics of the strains isolated in Rotterdam, show that Asian strains of PPNG seem at present to be endemic in the Netherlands. Spectinomycin was found to be effective in the treatment of patients with gonorrhoea due to PPNG strains.

Introduction

Penicillinase-producing strains of *Neisseria gonorrhoeae* (PPNG) have been reported from various countries throughout the world.¹ Occasional isolation of these organisms has been reported from several countries in Europe, but more cases have been reported from England and the Netherlands.¹ In England, the outbreak was successfully contained,² but in the Netherlands, especially since the beginning of 1979, the number of cases of PPNG infection has increased (Chief Inspector of Public Health, personal communication, 1979). The total number of cases of PPNG infection reported in the Netherlands—a country of 14 million inhabitants—between November 1976 and December 1978 was 65; the figures for the first and second quarters of 1979 were 59 and 60 respectively for cases of PPNG infection and 2390 and 2418 respectively for all reported cases of gonorrhoea. In the second quarter of 1979 2.5% of the number of reported cases of gonorrhoea over that period were due to PPNG infection. Because of underreporting of gonorrhoea and because a few cases of suspected and reported gonorrhoea are not confirmed by culture it is extremely difficult to calculate the exact relation between the number of cases of PPNG infection and the total number of cases of gonorrhoea in the Netherlands.

Similarly, a sudden increase in PPNG infections has been noted in Rotterdam. We observed 14 cases of gonorrhoea due to PPNG strains in the first five

months of 1979 compared with 13 cases seen in the preceding 26 months. This report describes the cases seen in Rotterdam between November 1976 and June 1979.

Patients and methods

Patients who attended the venereal disease clinic of the dermatovenereology department of the University Hospital, Rotterdam, between November 1976 and June 1979 with gonorrhoea due to PPNG strains were included in the study.

DIAGNOSIS

In addition to direct microscopy of Gram-stained smears from the urethra in men and the urethra and cervix in women, routine samples for culture on Thayer-Martin media were collected from the urethra and the throat in heterosexual men and from the urethra, the cervix, the rectum, and the throat in women. All the gonococcal strains isolated in our laboratory were routinely screened for PPNG by the method previously described by Phillips *et al.*³

Sensitivities of the PPNG strains to tetracycline, erythromycin, spectinomycin, and cefuroxime were performed by the agar dilution method.

Auxotyping was determined by the method described by Catlin.⁴ Plasmid DNA was isolated by a procedure described by Guerry and Falkow.⁵

TREATMENT

Twenty patients were treated with ampicillin or amoxycillin 3 g and probenecid 1 g orally in a single dose. Sixteen patients, including 13 patients who were still under observation, and who did not

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respond to ampicillin or amoxycillin, were treated with spectinomycin sulphate 3.2 g intramuscularly. Four patients were treated with cefuroxime 1.5 g intramuscularly.

Results

The epidemiological relationship of patients harbouring PPNG strains, their sex, profession, nationality, region of birth, and probable country of acquiring the infection are given in table I. Of the 27 cases seen in Rotterdam over the study period, 20 were in men and seven were in women. According to the history, patients 12 and 16 and patients 14 and 15 (table I) appeared to be related. Patient 23 infected a Dutch male patient, in whom only a non-PPNG strain could be isolated. However, this patient infected patient 24, who harboured a PPNG strain.⁶ Thus, epidemiologically, patients 23 and 24 appeared to be related.

Of the 17 patients who acquired their infection in the Netherlands only five (four female patients and one male patient) were infected in Rotterdam. The

other 12 patients were infected in The Hague and Amsterdam.

All 20 male patients were infected by prostitutes. Of the seven female patients, two were prostitutes and one was a bar-girl. Three housewives claimed to have been infected by their husbands or regular partners. One was infected by a casual Philippine friend (patient 23).

DIAGNOSIS

In the men, diagnoses were based on positive smear and culture results from the urethra in 19 cases and on a positive culture result from the urethra in one asymptomatic case. In the women, PPNG were isolated from the urethra in two cases, from the urethra and cervix in two cases, from the urethra, cervix, and rectum in one case, from the urethra, cervix, rectum, and throat in one case, and from the cervix alone in one case.

Of the 27 patients, only patients 1 and 2 acquired their infections directly in West Africa (table I). Eight patients (patients 3, 4, 5, 6, 17, 18, 22, and 23) were infected directly in South-east Asia.

TABLE I *Epidemiological data of patients harbouring PPNG strains isolated in Rotterdam*

Patient No	Occupation	Country of birth	Infection acquired
1 (M)	Sailor	West Africa	West Africa
2 (M)	Sailor	Ghana	Ghana
3 (M)	Sailor	Ivory Coast	Ivory Coast
4 (M)	Sailor	Northern Europe	South-east Asia
5 (M)	Sailor	Sweden	Hong Kong
6 (M)	Sailor	Norway	Thailand
7 (M)	Immigrant (civilian)	Norway	Philippines
8 (M)	Manual worker	Southern Europe	Philippines
9 (M)	Manual worker	Portugal	Western Europe
10 (M)	Manual worker	Mediterranean	The Netherlands
11 (M)	Student	Morocco	The Netherlands
12* (M)	Unknown	Spain	The Netherlands
13 (M)	Unknown	Greece	The Netherlands
14† (M)	Unknown	Turkey	The Netherlands
15† (F)	Housewife	Turkey	The Netherlands
16* (F)	Housewife	Turkey	The Netherlands
17 (M)	Non-immigrant (civilian)	Morocco	The Netherlands
18 (M)	Manual worker	Morocco	The Netherlands
19 (M)	Businessman	Morocco	The Netherlands
20 (M)	Businessman	Morocco	The Netherlands
21 (M)	Student	Western Europe	South-east Asia
22 (M)	Unknown	The Netherlands	Thailand
23‡ (F)	Air stewardess	The Netherlands	Thailand
24‡ (F)	Housewife	The Netherlands	Western Europe
25 (F)	Bar girl	The Netherlands	The Netherlands
26 (F)	Prostitute	The Netherlands	The Netherlands
27 (F)	Prostitute	The Netherlands	The Netherlands

* † ‡ Epidemiologically related

BIOLOGICAL CHARACTERISTICS OF PPNG STRAINS

The biological characteristics of PPNG strains isolated in Rotterdam are given in table II.

Non-PPNG strains were also isolated in seven patients harbouring PPNG strains; three (patients 3, 5, and 23) were infected directly in South-east Asia and three (25, 26, and 27) were highly promiscuous prostitutes. Except for patients 10 and 25, all simultaneous isolations of PPNG and non-PPNG strains in the same patient occurred in 1976 and 1977.

Auxotypes

In the patients directly infected in West Africa arginine-requiring strains were isolated whereas in the eight patients infected directly in South-east Asia proline-acquiring and zero/wild strains were isolated. In two strains no auxotyping was performed.

Plasmids

PPNG strains from patients directly infected in West Africa had a cryptic plasmid of 2.5×10^6 daltons and a penicillinase-producing plasmid of 3.3×10^6 daltons. No transfer plasmid was found. PPNG strains from eight patients directly infected in South-east Asia had a cryptic plasmid of 2.5×10^6 daltons

and a penicillinase-producing plasmid of 4.5×10^6 daltons. Five of the eight PPNG strains had a larger transfer plasmid of $\pm 24 \times 10^6$ daltons. The three patients harbouring South-east Asian PPNG strains without transfer factor were all seen in 1977.

Of the other patients not directly infected in West Africa or South-east Asia, only the two highly promiscuous prostitutes (patients 26 and 27) had auxotypes and plasmids of the West African PPNG strain-type. Neither prostitute appeared to have spread the PPNG strain she was harbouring.

Auxotypes and plasmids of the South-east Asian PPNG strain-type were found in all the other patients. A transfer plasmid could not be found in only one PPNG strain (patient 25). In the two epidemiologically related Turkish patients (12 and 16) different auxotypes were found; a comparison of plasmids was not possible in this case.

SENSITIVITIES

The PPNG isolates appeared to be less sensitive to tetracycline and cefuroxime than did other gonococcal strains isolated recently from patients in our outpatient department. Because of the small number of PPNG isolates statistical analysis has not been carried out to prove this finding. For the same reason no statistical comparison of distribution of

TABLE II *Biological characteristics of PPNG strains isolated in Rotterdam*

Patient No	Non-PPNG strains	Auxotypes	Plasmids (daltons)				MICs ($\mu\text{g/ml}$) to				Country of direct infection
			Cryptic 2.5×10^6	3.3×10^6 (African)	4.5×10^6 (Asian)	Transfer $\pm 24 \times 10^6$	T	E	S	C	
1 (M)		Arginine	+	+	-	-	1	4	8	ND	W Africa
2 (M)		Arginine	+	+	-	-	2	2	8	ND	W Africa
3 (M)	+	Proline	+	-	+	-	4	2	8	ND	S-E Asia
4 (M)		Proline	+	-	+	-	1	4	8	ND	S-E Asia
5 (M)	+	Proline	+	-	+	+	1	0.25	4	0.25	S-E Asia
6 (M)		Zero/Wild	+	-	+	+	1	1	8	ND	S-E Asia
7 (M)		Proline	+	-	+	+	1	1	8	0.12	S-E Asia
8 (M)		Proline	+	-	+	+	2	1	8	0.25	S-E Asia
9 (M)		Proline	+	-	+	+	4	2	8	0.25	S-E Asia
10 (M)	+	Proline	+	-	+	+	2	2	8	ND	
11 (M)		Proline	+	-	+	+	4	4	8	0.25	
12* (M)		Proline	ND	ND	ND	ND	2	1	8	0.12	
13 (M)		Proline	+	-	+	+	2	1	8	ND	
14† (M)		Proline	+	-	+	+	1	0.12	8	0.12	
15† (F)		Proline	+	-	+	+	0.25	0.12	8	0.12	
16* (F)		Zero/Wild	+	-	+	+	4	1	16	0.12	
17 (M)		ND	+	-	+	+	2	8	8	ND	S-E Asia
18 (M)		Proline	+	-	+	+	2	8	8	0.25	S-E Asia
19 (M)		Proline	+	-	+	+	2	2	8	ND	
20 (M)		Zero/Wild	+	-	+	+	2	2	8	0.25	
21 (M)		Proline	ND	ND	ND	ND	2	0.25	8	0.25	
22 (M)		ND	+	-	+	+	1	0.5	8	0.12	S-E Asia
23‡ (F)	+	Zero/Wild	+	-	+	+	1	0.25	16	ND	S-E Asia
24‡ (F)		Zero/Wild	+	-	+	+	1	0.25	16	ND	
25 (F)	+	Proline	+	-	+	-	4	1	8	0.5	
26 (F)	+	Arginine	+	+	-	-	1	2	8	ND	
27 (F)	+	Arginine	+	+	-	-	0.5	0.25	16	ND	

* † ‡ Epidemiologically related

+ Positive - negative

ND = not done (strain died)

T = tetracycline; E = erythromycin; S = spectinomycin; C = cefuroxime

sensitivities to the four antibiotics between West African strain-type and South-east Asian strain-type isolates has been made.

Comparison of the distribution of sensitivities to erythromycin was not possible because no gonococcal strains isolated from patients in our outpatient department had been tested previously for sensitivity to this antibiotic.

All PPNG isolates were sensitive to spectinomycin (MIC between 4 and 16 µg/ml). The sensitivity patterns in the epidemiologically related strains (patients 23 and 24) were identical. A one-dilution-step difference was noted in the sensitivities to tetracycline and spectinomycin between the strains from patients 12 and 16. The two-dilution-step difference in sensitivity to tetracycline between strains from patients 14 and 15 might be explained by accepting an MIC of 0.50 µg/ml as the true MIC.

FOLLOW UP

Of the 20 patients treated with ampicillin or amoxycillin, five did not return for follow up. In 13 of the 15 cases who were available for follow up there was treatment failure; in two cases no gonococci could be isolated on the seventh day after treatment. Of the 16 patients treated with spectinomycin two did not return for follow up; treatment was successful in the remaining 14. Of the four patients treated with cefuroxime, one did not return for follow up and treatment was successful in the remaining three.

Discussion

The epidemiological data on our patients with gonorrhoea due to PPNG strains are strikingly similar to those on patients with chancroid seen in our clinic.⁶ Most patients with chancroid could be classified in four main groups according to nationality: Dutch, Portuguese, Turkish, and Moroccan. Of these patients, 89% acquired their infections from prostitutes. Of the total of 53 patients, 50 were men and three were women (all of whom were prostitutes). The role of prostitutes in the spread of PPNG strains has been stressed previously¹ and has been confirmed by our data on the source of infection, as mentioned by our male patients.

Before 1977 chancroid and gonorrhoea due to PPNG strains were mostly imported by sailors and by airline personnel. It is only since 1977 that chancroid and PPNG infections have been acquired in the Netherlands. The rising incidence of chancroid in Rotterdam was noted in 1977 and 1978; the first PPNG infections in the Netherlands (Rotterdam) were recognised at the end of 1976 and the rise in

incidence of cases of PPNG infection was seen in 1978 and 1979.

From an epidemiological point of view PPNG infections are behaving more like chancroid than like gonorrhoea due to non-PPNG strains. In our clinic only a few infections with gonorrhoea due to non-PPNG strains in male patients are acquired by sexual contact with prostitutes.

An important feature of our patients is that importation of PPNG strains from West Africa and South-east Asia no longer plays a major role. Apart from Dutch civilians, the most important group of patients has become the immigrant workers from the Mediterranean countries.

The isolation of both PPNG and non-PPNG strains in seven of our 27 patients may indicate plasmid instability in some PPNG strains. Such strains were isolated in the first year of our investigation more often than in the remaining period.

Interestingly, PPNG strains with the characteristics of African PPNG strains did not spread, even in those instances where highly promiscuous prostitutes were concerned. This may be due to the instability of the penicillinase-producing plasmid involved or to the fact that these African strains lack a larger "stabilising" transfer plasmid of 24×10^6 daltons.

As far as conclusions can be drawn from our limited material in Rotterdam, mainly plasmid-stable PPNG strains with characteristics of PPNG strains from the Philippines containing transfer plasmids are circulating in the Netherlands. The fact that these strains seem to be less sensitive to tetracycline and cefuroxime than non-PPNG strains isolated in Rotterdam is alarming. PPNG strains which are less sensitive to several antibiotics have been reported previously—namely, those isolated in the Philippines and South-east Asia.¹

Auxotyping and plasmid identifications seem to be useful in studying the epidemiology of PPNG infections, as has been shown by this study. Additional studies of sensitivity are necessary to maintain or to alter existing treatment schedules. In our study all PPNG isolates were sensitive to spectinomycin, and spectinomycin sulphate 3.2 g intramuscularly proved to be effective in treating patients with infections due to PPNG strains. The number of patients treated with cefuroxime was too small to evaluate the results.

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References

1. Perine PL, Morton RS, Piot P, Siegel MS, Antal GM. Epidemiology and treatment of penicillinase-producing *Neisseria gonorrhoeae*. WHO/VDT/79.419. WHO/VDT/RES/GON/79.122.
2. Arya OP, Rees E, Percival A, Alergant CD, Annels EH, Turner GG. Epidemiology and treatment of gonorrhoea caused by penicillinase-producing strains in Liverpool. *Br J Vener Dis* 1978;54:28-35.
3. Phillips CW, Aller RC, Cohen CN: Penicillinase-producing *Neisseria gonorrhoeae*. *Lancet* 1976;ii:960.
4. Catlin WB. Nutritional profiles of *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Neisseria lactamica* in chemically defined media and the use of growth requirements for gonococcal typing. *J Infect Dis* 1973;128:178-94.
5. Guerry PD, LeBlanc DJ, Falkow S. General method for isolation of plasmid deoxyribonucleic acid. *J Bact* 1973;116:1064-6.
6. Nayyar KC, Stolz E, Michel MF. Rising incidence of chancroid in Rotterdam. Epidemiological, clinical, diagnostic and therapeutic aspects. *Br J Vener Dis* 1979;55:439-41.