CONTINUING MEDICAL EDUCATION

PENICILLINASE PRODUCING *NEISSERIA GONORRHOEAE* (Epidemiology and management)

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Historical background

Drug resistant strains of *Neisseria gonorrhoeae* were present in 1930s. Eight percent of the gonococcal strains collected in Denmark before 1937 were resistant at that time to 50 μ gml of sulphapyridine.[1] This gonococcal resistance continued throughout the 1940s resulting in a decline in the usefulness of sulphonamides for the treatment of gonorrhoea. So much so that, by the end of 1940s, about 90% of the gonococcal isolates showed increased resistance to sulphonamides and an approximately same proportion of patients with gonorrhoea failed to be cured with sulphonamides.[2] Before the extensive use of penicillin for gonorrhoea, virtually all gonococci were susceptible to less than 0.03 units/ml of penicillin.[3,4] However, with the widespread use of slow-release-penicillins such as PAM (procaine penicillin in oil with aluminium monostearate), chromosomal mutations started occurring with the resulting increase in resistance to penicillin.[5] Penicillin resistance was first reported in 1955 and subsequently many reports followed from various parts of the world including India. In 1955, in the United States, only 0.6% of the gonococcal isolates required more than 0.05 units/ml of penicillin to inhibit the growth of the organism, but by 1965 this proportion had increased to 42%.[6] A gradual increase in resistance has been reported from Delhi (India) (12.8% in 1969-73, 30.23% in 1976-77, 37.32% in 1977-78 and 50.50% in 1978-79) as well.[7] At Madras (South India) 23.4% of the strains isolated between April 1963 and September 1964, and 60.4% of the strains isolated between October 1964 and September 1965 were found to be resistant.[8] A similar study in 1970 revealed 90% of the strains to be resistant to penicillin.[9] At Bombay too the incidence of resistant strains isolated during 1968-69 was reported to be 56% to penicillin, 64.8% to spiramycin, 50% to erythromycin and 27.8% to tetracycline.[10] At Delhi in 1978-79, 60.39% of the gonococcal isolates were resistant to ampicillin. Forty seven percent strains exhibited simultaneous resistance to 2 or more drugs.[11]

The problem of penicillin resistance has been further compounded by the appearance of penicillinase producing strains of *Neisseria gonorrhoeae* (PPNG). Strains of PPNG first emerged in the Far East and West Africa in the year 1975. In the United States the first two cases were identified in March-April 1976 who had had sexual contact in the far east before returning to the United States.[12] The first British case was detected in September 1976,[13] which was followed by an out-break of 80 cases after 2 months in Liverpool.[14] In India the first case of PPNG was detected in 1979-80 at Vishakhapatnam (South India).[15] The first cases of PPNG from north India were detected in 1982-83, at Chandigarh.[16] Since then a total of 15 cases have been detected at the same centre with an incidence rate of

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12.2%.[17] Similar studies conducted at Delhi[7] in 1978-79 and at Bombay[18] in 1980 failed to demonstrate penicillinase producing strain of *Neisseria gonorrhoeae*.

Plasmid types

The Far Eastern isolates were originally found to contain two plasmids with a molecular weight of 4.4 and 24.5 mega daltons, while the African strains of PPNG contained a smaller sized plasmid of 3.2 mega daltons. Recently, cases in Africa (Ghana and Kenya) have been described with isolates containing the 4.4 mega dalton (Asian) plasmid.[19] The 3.2 and 4.4 mega dalton plasmids are the resistance (R) factors which code for beta-lactamase (penicillinase) production. The larger (24.5 mega dalton) plasmid is a conjugative or transfer factor which enables the resistance to be transferred to other gonococci and other organisms. The R plasmids are readily lost on subculture in vitro unless this is carried out in the presence of penicillin or ampicillin.[19] The other types of plasmid detected in *Neisseria gonorrhoeae* are 24 mega dalton plasmid,[20] 6.6 kilobase R plasmid[21] and 4.9 kilobase R plasmid.[22] An analysis of the plasmid types of PPNG in Liverpool showed that even though all the cases in 1976 and 1977 contained only the 3.2 mega dalton plasmid, this had changed by 1982. In that year 54 cases were found with the following plasmids : 4.4 mega dalton plasmid alone (31 cases), 3.2 mega dalton plasmid alone (15 cases), 3.2 mega dalton and 24.5 mega dalton plasmids (5 cases) and 4.4 mega dalton and 24.5 mega dalton plasmids (3 cases).[23]

Prevalence of PPNG.

By the year 1986 penicillinase producing *Neisseria gonorrhoeae* strains had been identified in 56 countries and epidemiologic evidence suggests their presence in at least another 40 countries.[19]

(a) Far East and Africa

The prevalence of PPNG is highest in south East Asia and Africa. And this is increasing in an alarming fashion in these two endemic areas. At Singapore, the prevalence of PPNG has increased from 0.3% in 1977 to 19.2% in 1980 and 30% in 1981.[24] Similarly, in Thailand the prevalence of PPNG has increased from 8.6% in 1978 to 28.8% in 1980 and 42% in 1981.[25]

The African data are more sparse but support the general trend of an increasing prevalence of PPNG.[26] At Nigeria and Kenya, the prevalence of PPNG has increased from 3% in 1977 to 20% in 1980 and from 0% in 1980 to 20% in 1982 respectively. At Ghana the prevalence of PPNG in 1982 was 32%.[19]

(b) The United States

The first case of gonorrhoea with PPNG was detected in 1976, and since then the number of cases has increased. Between 1976 and 1979 the number of cases increased slowly, mostly occurring in the people or their sexual partners who had travelled to the Far East. After 1979 the number of cases started to rise rapidly. In 1979 the number of reported cases were 328 and this rose to 4457 by 1982 and then declined to 3720 by 1983. Despite this alarming increase, the proportion of PPNG isolates to non-PPNG was less than 0.5%.[19] This overall prevalence hides the fact that rates vary throughout the United States. Some areas of America, such as New-York city, California and Florida, where the endemic transmission is mainly responsible for the continued prevalence of PPNG, account for 60% of all PPNG in the United States.[19]

(c) The United Kingdom

Since the first case report in the United Kingdom (UK) in 1976, the number of cases and prevalence rates have increased.[27,28,29] The prevalence of PPNG has increased from 0.02% in 1977 to 1.7% in 1982.[30] These national data, however, hide the regional differences. The prevalence rate was highest in the ports and the tourist areas.[31] Monthly variations in the prevalence were as much as from 0.95%

to 10.2% in a central London clinic.[32] Until 1980 the rise in PPNG had resulted largely from the directly imported cases and the ratio of these to the indigenous cases was constantly running at about 2 : 1. This suggests that increasing importation, and not the sustained transmission within the country was the reason for the substantial increase in incidence. In 1980 a shift from the imported to the endemic transmission occurred. Between 1980 and 1981 the indigenous cases increased by 230% while imported cases increased by only 53%.[33] An examination of the characteristics of the people who were infected with PPNG shows that these strains are mainly imported by male airline passengers who had recently been infected in endemic areas. It was found that the infection with directly imported strains had occurred predominently in men (male to female ratio was 9 : 1), but the indigenous strains were divided nearly equally between the two sexes (male to female ratio of 1.7 : 1).[19] The short incubation period of gonorrhoea and the slow and infrequent rail or sea connections to the endemic areas made air travel the only plausible mode of transmission. It was also found that men and women who imported PPNG were typically older than those infected with indigenous PPNG strains.[19] Most PPNG reaches the UK from two primary endemic regions. Over the last 7 years, 42% of the cases were derived from the Far East, 35% from Africa and remaining 22% from Europe and other sources.[19]

(d) Europe

Apart from the United Kingdom, Holland is the only european country which has reported a substantial number of cases, in particular in Hague and Amsterdam. In Holland, the first case of PPNG was reported in 1977.[19] The prevalence has been found to vary throughout the country. The highest rates in 1982 were found in Hague (23%) and Amsterdam (11%).[34] Four plasmid patterns were described. The isolation rate from homosexuals was low, 2.6% of all the strains occurring in this group of patients.[31]

In scandinavian countries the prevalence of PPNG is low. Denmark reported its first case in 1977. The number of cases rose to 129 by 1983 with a prevalence of 1.2%. Twenty two percent of infections were acquired in the Far East, but the majority were acquired within Denmark.[35] Other scandinavian countries such as Finland, Iceland, Norway, Sweden show similar low prevalence rates for PPNG.[19]

(e) India

The first case of PPNG was detected in 1979-80 at Vishakhapatnam (South India).[15] Three of the 114 isolates during 1979-1980 were detected to be PPNG strains. From north India, the PPNG strains were detected in 1982-83 at Chandigarh.[16] Since then a total of 15 cases have been detected from the same centre with a prevalence rate of 12.2%.[17] Vijayalakshmi et al reported a case of PPNG from Madras in 1982.[36] Penicillinase producing *Neisseria gonorrhoeae* has also been detected in eastern India.[37]

Factors encouraging the development of PPNG

The development of penicillinase producing strains and the subsequent development of spectinomycin resistance is in large part due to the use of suboptimal doses of antibiotics. The indiscriminate use of antibiotics tends to occur in countries with poor medical service lacking in an infrastructure of a comprehensive STD service run by specialists in that field. In the United Kingdom, for example, 90% of STD care is provided by specialists, in the United States 20%, and in developing countries about 1% of cases. In many areas the drugs important in the treatment of sexually transmitted diseases are available over the counter and used in less than the recommended dosages.[38] Treatment without any attempt at examination and diagnosis, and chemoprophylaxis were important factors responsible for the development of

PPNG strains. In a study of 777 prostitutes at Singapore, penicillin was detected in the urine of 99 (12.7%) prostitutes. The rate of gonococcal infections in these women was half (5.1%) than those not using prophylactic penicillin (11.2%). The prevalence of PPNG in those taking prophylactic penicillin was 40% compared to 26.5% in those not taking prophylactic penicillin. The sources for purchase of penicillin and other antibiotics were private doctors (23%), unlicensed medical shops (22%), drug peddlers within brothels (9%) and the remainder from friends and colleagues.[39]

Clinical manifestations of infection with PPNG

The same sites such as urethera, rectum, cervix and pharynx are infected as with ordinary *Neisseria gonorrhoeae* infections, with similar clinical manifestations. However, the prevalence of PPNG infections is low in homosexuals.[40,32,41] Some reports indicate that pelvic inflammatory disease occurs relatively more frequently with PPNG strains. This higher rate of pelvic inflammatory disease in some series is difficult to interpret, especially since other workers have shown that this complication is no higher than in those women suffering from ordinary gonococcal infections.[42] In an out-break of PPNG in Los Angeles in 1980, 21.2% of women infected had pelvic inflammatory disease (PID) in comparison to 10-18% normally seen with ordinary *Neisseria gonorrhoeae* infection.[43,44]

Cases of ophthalmia neonatorum caused by PPNG have been reported in the Far East and United Kingdom.[45,46,47] These were case reports and it is not possible to say whether this complaint is greater than one would expect with non-penicillinase producing strains.

Tests for penicillinase producing gonococci

While the presence of penicillinase producing gonococci may be strongly inferred from the results of disc diffusion method, the following tests are confirmatory.

Iodometric technique[69]

A suspension of gonococci is made in a solution of penicillin in a small test tube or well of a microdilution plate, stirred and incubated for half an hour. A small drop of starch solution is added and mixed followed by a drop of iodine solution. A blue colour develops which rapidly disappears if rotated for 1 minute if penicillinase is present.

Acidometric technique[69]

Using a small test or capillary tubes or microdilution plates, a buffered solution of penicillin with neutral red as indicator is adjusted to pH of 8.5 by drop-by-drop addition of sodium hydroxide giving it a dark red to purple colour. A heavy suspension of the gonococcal culture under test is made in this solution which turns yellow if penicillinase is present.

Chromogenic cephalosporin technique[69]

Gonococci from colonies on plates, in broth culture or as suspension of intact or sonicated lysed cells will, if penicillinase producing, cause solution of a test chromogenic cephalosporin compound to turn red. Test strips for direct use on culture plates are also available.

Recently a fluorescent spot test has been developed which detects penicillinase in the uretheral exudates. This is a rapid, inexpensive and fairly sensitive and specific test.[48]

Treatment

Spectinomycin was the first drug used in the treatment of patients with PPNG infections and is still the mainstay of treatment in such cases. The dosage used and failure rates varied. One gram intramuscularly in 189 female patients gave a failure rate of 4.8%.[49] Two grams intramuscularly in two different series gave failure rates of 4.3% and 3.7%.[42,50] But when 4 grams is used intramuscularly there were no failures.[50] Further studies since then have shown no failures using 2 grams when used in Far East and the Philippines.[51,52]

The cephalosporins particularly cefoxitin, cefuroxime and cefotaxime have also been used for the treatment of PPNG infection. The failure rates range from 0-1.8%.

Cefoxitin

It can be administered in a dose of 1-2 grams in combination with 1 gram of probenecid. A small series of 12 patients treated with 1 gram of cefoxitin in Far East showed no failures.[19] Other series with the use of 2 grams also show no failures.[53] Currently 2 grams is considered the most appropriate dose of cefoxitin for the treatment of uncomplicated infections with PPNG.

Cefuraxime

Good cure rates have been achieved using a dose of 1.5 grams of cefuroxime.[52,54]

Cefotaxime

It has been used effectively in PPNG infections at doses ranging from 0.5-1 gram intramuscularly. In England no failure were recorded using 0.5 gram.[55] In Singapore a dose of 1 gram resulted in a failure rate of 1.8%,[56] and with the same dose no failure were found in 31 patients in the western Pacific.[57]

In certain instances, first line therapy with spectinomycin may not be so effective. In pelvic inflammatory disease, spectinomycin can be used in doses of 2 grams intramuscularly twice a day. But many clinicians favour the cephalosporins, for example cefuroxime 1.5 grams with 1 gram of probenecid followed by 0.75 grams 8 hourly. A disseminated gonococcal infection due to PPNG could also be treated with this regime, or with 0.5 gram cefotaxime four times daily intramuscularly for 5 days,[58] or finally as recommended by centres for disease control, with cefoxitin 1 gram or cefotaxime 500 milligrams four times a day intravenously for atleast 7 days.

Pharyngeal infections are often hard to eradicate, whether the organism is penicillinase producing or not. In pharyngeal PPNG infections spectinomycin is not as effective as the cephalosporins and its use can give failure rates as high as 80%. In view of this either cotrimoxazole, 9 tablets as a single dose daily for 5 days,[59] or a course of a cephalosporin, for example cefuroxime 0.75 gram daily for 3 days have been recommended.[60]

Other drugs which have been or being evaluated in the treatment of PPNG infections are gentamicin,[61] kanamycin,[62] a combination of clavulanic acid and amoxycillin (augmentin),[63] moxalactam,[64] rosaramicin,[65] rosoxacin,[51] thiamphenicol[19] and aztreonam.[66]

Spectinomycin resistant PPNG are now recognised,[67,68] but are not prevalent enough to suggest a switch over from this first line drug. It illustrates the importance of continued microbiological surveillence of all cases of gonorrhoea, PPNG or not, and the use of adequate doses of the chosen antibiotic preferably given under supervised conditions.

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