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Full Length Research Paper

An investigation on antibiotic resistance of *Neisseria gonorrhoeae* isolated from gonorrheal patients in Zahedan, Iran from 2007 to 2010

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Present study was aimed to determine antibiotic susceptibility and penicillinase production by *Neisseria gonorrhoeae* strains isolated from gonorrheal patients in Zahedan (south-east Iran). In a descriptive study from 2007 to 2010, 400 suspected patients were studied by history review, medical examination, Gram staining and culture in Thayer-Martin medium. Antibiotic susceptibility test of isolated strains was done by disk diffusion method and penicillinase test in penicillin resistant isolates by aciodometric method. The culture of 77(19.2%) of gonorrheal patients were positive. The resistance rate against applied antibiotics was as follow: penicillin (79.2%), ciprofloxacin (53.2%), ceftriaxone (3.8%), spectinomycin (2.5%), cefixim (12.9%), co-trimoxazole (93.5%), tetracycline (88.3%) and gentamicin (29.8%). In the meantime, 83.1% of penicillin resistant isolates produced penicillinase enzyme. Ceftriaxone, spectinomycin and cefixime are the sole antibiotics that could be considered as selective drugs. Quinolones which were regarded as an effective group of antibiotics until recently, haven lost their efficacy. Resistance against other antibiotics is rapidly growing, thus, conducting experimental tests and determination of minimum inhibitory concentration and clinical trial studies at fixed intervals can contribute to diagnosis of resistance of gonococci and rapid and successful treatment of their infections.

Key words: *Neisseria gonorrhoeae*, gonorrhea, penicillinase (β-lactamase).

INTRODUCTION

Gonorrhea is a transitional infection of columnar epithelium which is caused by *Neisseria gonorrhoeae* that is a diplococcus gram negative organism. The latter is the second most responsible bacterium for systemic and venereal infections after *Chlamydia trachomatis* (Handsfield et al., 2005). In accordance with current data, isolation of *N. gonorrhoeae* from STDs victims varies from 4.6 to 64.7% throughout the world (Tapsall, 2002; Hansen et al., 2003) whereas, this figure in Iran lies between 1.9 and 18% (Ghasemian-Safaii, 1989; Shakibaie et al., 2008). Nevertheless, thorough cure of gonorrhea necessitates rationalized information on drug resistance pattern of the various strains of the organism. The concluding issue helps not only in reduction of treatment expenditure but also lessens chances of therapy failure.

In recent years antibiotics resistance prototype of *N. gonorrhoeae* has constantly changed as a result of inappropriate use of drugs (Ye et al., 2002) and the gonococci have shown enormous resistance against routine antibiotics formerly used for treatment of gonorrhea (Zheng., 2003). In this regard, emergence of new strains of penicillinase-producing gonococci (PPNG) as well as other strains, which are all resistant against certain antibiotics including: spectinomycin, tetracycline, ciprofloxacin and cefexim have created massive concern in the world of medicine (Handsfield et al., 2005). Hence, in Iran we have insufficient information vis-à-vis drug resistance pattern of gonococci strains and their relevant β-lactamase production. Surprisingly, most laboratories

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Table 1. Frequency distribution of gonococci according to gender of the victims.

Gender	Results					
	Positive		Negative		Total	
	Number	Percent	Number	Percent	Number	Percent
Men	66	16.5	292	73	358	89.5
Women	11	2.7	31	7.7	42	10.4
Total	77	19.2	323	80.7	400	99.9

do not carry out sensitivity test for the bacteria in question and therefore, the medics should inevitably rely on provincial or national epidemiologic data for treatment protocol of gonococci strains that in most cases the outcome is failure of remedy.

In accordance with earlier stated points, we do believe that in every geographic region, epidemiologic study of gonococcal strains and surveillance for their most recent resistance disparity against certain antibiotics along with mode of development of such phenomenon is mandatory.

The current study was firstly intended to isolate gonococci from suspected individuals and secondly to investigate the latest resistant pattern of the isolated strains and eventually, assessment of β-lactamase production by resistant strains amongst gonorrheic persons in Zahedan.

MATERIALS AND METHODS

This cross-sectional study was carried out during 2006 to 2009 by simple sampling amid 400 gonorrheal suspects who were directed to reference laboratory of Shahid Razmjoo Moghadam in Zahedan by medics. All patients that is 358 males and 42 females, had symptoms of purulent urethritis and cervicitis.

Isolation of *N. gonorrhoeae*

For this purpose, samples from urethra and endocervix were cultured directly on chocolate agar and modified Thayer-Martin agar that is basic GC agar plus 2% hemoglobin and supplements of vancomycin, colistin, nystatine and trimethoprim. The plates were then incubated at 35°C for 48 h under humid and microaerophilic conditions. When the incubation was over, the identification of the colonies in line with their morphology (pin pointed, transparent and mucoid form) gram staining, oxidase and catalase tests were performed. Furthermore, other confirmatory tests included: glucose fermentation and non-hydrolysis of maltose in cystein tripticase base agar containing of 1% sugar and eventually co-agglutination with monoclonal antibodies were carried out.

The isolated strains were inoculated in 1 ml of brain heart infusion medium containing 20% glycerol for further investigations.

Antibiotic sensitivity tests

In order to achieve this objective, the isolated strains were subjected onto sensitivity tests vis-à-vis certain antibiotic disk as: penicillin (10 U/disk), ciprofloxacin (30 µg/disk), ceftriaxone (30 µg/disk), spectinomycin (30 µg/disk), co-trimoxazole (200 µg/disk), cefexim (30 µg/disk), tetracycline (30 µg/disk) and gentamicin (10 µg/disk). The procedure applied for interpretation was disk diffusion in Mueller-Hinton agar consisting 10% defibrinized blood of sheep according to National Committee for Clinical Laboratory Standards (NCCLS) protocol. Moreover, for assessment of isolated strains' β-lactamase activity, acidometric method was employed (Sng et al., 1981). So as to present the data, frequency tables in addition to mean indices and standard deviations were applied and for analysis of data we exploited SPSS software. All the results were calculated according to confidence interval of 95% and $P<0.05$.

RESULTS

Out of 400 samples taken from urinary tracts, 77 cases were proved to be *N. gonorrhoeae* hence, isolation rate was 19.2%. Of this figure 89.5% of the victims were male and 10.4% female (Table 1).

As the table indicates, out of 77 positive samples 66 belonged to men (that is 85.7%) and the remaining 11 to women (14.3%). The latter shows that, frequency of gonococci in men was 66 out of 358 (18.4%) whereas; in women the figure was 11 out of 42 (26.1%). Furthermore, about 43.5% of the affected individuals were between 26 to 35 years of age and 24.5% were ranged amid 36 to 45 years nevertheless, most of the positive cases in both genders were between 26 to 35 years (7.5% males and 1.5% females), Table 2.

In accordance with drug resistance against certain antibiotics, the distribution was as: co-trimoxazole 93.5% (72 cases), tetracycline 88.3% (68 cases), penicillin 79.2% (61 cases), ciprofloxacin 53.2% (41 cases), cefexim 12.9% (10 cases), ceftriaxone 3.8% (3 cases) and lastly spectinomycin 2.5% (2 cases). The overall findings are shown in Table 3.

In addition, 64 out of 77 investigated strains were found positive that is 83.1% of diagnosed gonococci produced penicillinase (PPNG).

Out of total 77 gonococci strains in this study, 53 (68.8%) possessed multiresistant property, which showed resistance to at least three classes of antibiotics either totally or partially.

DISCUSSION

In accordance with data published by WHO, prevalence of gonorrhea in developing countries are about twenty times more than developed countries (Agacfidan and Kohl, 1999).

In our investigation, about one fifth of the patients

Table 2. Frequency distribution of gonococci grouped by age and gender.

Gender		Age range plus percentage				
		15-25 (%)	26-35 (%)	36-45 (%)	>45 (%)	Total (%)
Men	Positive	18(4.5)	30(7.5)	16(4)	2(0.5)	2(0.5)
	Negative	58(14.5)	126(31.5)	73(18.2)	35(8.7)	292(73)
	Total	76(19)	156(39)	89(22.2)	37(9.2)	358(89.5)
Women	Positive	4(1)	6(1.5)	1(0.2)	0	11(2.7)
	Negative	9(2.2)	2(3)	8(2)	2(0.5)	31(7.7)
	Total	13(3.2)	18(4.5)	9(2.2)	2(0.5)	42(10.5)
Cumulative		89(22.2)	174(43.5)	98(24.5)	39(9.7)	400(100)

Table 3. Antibiotics-related reactions of gonococci strains through disk diffusion method.

Antibiotic	Sensitive		Semi-sensitive		Resistant	
	Number	Percent	Number	Percent	Number	percent
Penicillin	11	14.2	5	6.6	61	79.2
Ciprofloxacin	28	36.3	8	10.5	41	53.2
Ceftriaxone	62	80.5	12	15.7	3	3.8
Spectinomycin	59	76.6	16	20.9	2	2.5
Cefexim	60	77.9	7	9.1	10	12.9
Co-trimoxazole	3	3.9	2	2.5	72	93.5
Tetracycline	6	7.7	3	4	68	88.3
Gentamicin	49	63.6	5	6.6	23	29.8

under study suffered from gonorrhea and 85% of them were male. The highest rate of resistance was against co-trimoxazole, tetracycline and penicillin, besides most of the strains were penicillinase positive and resistant to at least three antibiotics simultaneously. Therefore, rate of gonococci isolation in the current study corresponds to other cities in Iran including; Kerman and Arak (Shakibaie et al., 2008; Ghaznavi et al., 1999). However, in the various investigations throughout the world, incidence of gonorrhea has been reported between 4.6 to 64.7% (Tapsall, 2002; Hansen et al., 2003).

Our findings demonstrated that, most of the strains were resistant to penicillin and almost 83.1% of them produced penicillinase, the latter corresponds with other studies in different cities of Iran, indicative of increasing trend of resistance to the former antibiotic (Shakibaie et al., 2008; Ghaznavi et al., 1999; Erfanian et al., 2005).

As WHO reported in 2000 the rate of resistance of gonococci to penicillin in south-east Asian countries was as high as 48 to 91% (WHO, 2001). Similarly, in another study in Russia, three quarter of gonococci was resistant to penicillin (Vorobieva et al., 2007). One of the reasons behind this resistance could be availability of penicillin and familiarity of the victims, secondly self-treatment might be due to certain attitudes amongst different cultures and individuals that cause hesitation of the sufferers to consult with a medic, various chronic and untreated cases are definite instances of the former dispute (Shakibaie et al., 2008; Ghaznavi et al., 1999; Zarggoshi, 2002).

Very few studies regarding penicillinase positive strains that have been carried out in Iran, indicates emergence and spread of such strains enormously. More than half of resistant strains of gonococci in Kerman have been reported β-lactamase positive (Shakibaie et al., 2008), whereas this figure in Arak has increased to three quarters (Ghaznavi et al., 1999). Since the revelation of penicillinase producing strains of gonococci in West Africa and Asia during 1976, such strains have spread immensely throughout the world as nowadays more than half of such strains in Africa, Asia and Latin America are penicillinase positive (WHO, 2001). Similarly, another study in China has shown that 6.9% of gonococci strains are penicillinase producer and this number is increasing (Zheng et al., 2003) in a way that, a very recent study has demonstrated that distribution of PPNG strains from 8% in 1999 has increased to 57% in 2004 (Su et al., 2007). In India too, 20% of gonococcal strains were stated penicillinase positive (Khaki et al., 2007) surprisingly enough, according to investigations in Russia none of gonococci was penicillinase producer (Vorobieva et al., 2007). The latter seems very weird since regional and

global data indicate differently nevertheless, the researchers have not expressed any reason for former findings.

As gonorrheal therapy by kinolones recommended by CDC in 1989 the drugs of choice were ciprofloxacin and ofloxacin (Zheng, 2003) nonetheless, by extensive use of such antibiotics in different countries the rate of resistance too, increased worldwide in general and in south-east Asia in particular.

In this study, the rate of ciprofloxacin resistant strains (QRNG) was 53.2% although, different studies throughout the world as well as various parts of Iran have shown a mixture of resistance for instance; this rate for other cities in Iran as; Sari, Kerman and Mashhad was 7, 22 and 46% respectively (Nasrolahi, 1999; Shakibaie et al., 2008; Erfanian et al., 2005) while for Arak it was nil (Ghaznavi et al., 1999). According to similar studies in Birmingham, France, Russia, Germany and Vietnam the percentage of resistance to ciprofloxacin have been reported quite variably that is 2, 5.3, 17, 47.7 and 100% correspondingly (Castor et al., 2001; Herida et al., 2004; Vorobieva et al., 2007; Enders et al., 2006; Cao et al., 2008). Regarding this phenomenon Chinese have described almost zero percent of resistance to ciproloxacin in 1994 whilst, this rate increased to 83.9% in 1999 and to 98.9% in 2006 (Su, 2007). In India too, the resistance has been stated 67.3% during 2002 (Bala et al., 2003) the concluding has increased to 98% in 2006 (Khaki et al., 2007). In other countries including Hong Kong, Japan and Australia speed of resistance is also remarkable (Tapsall, 2002; WHO, 2001; Jain et al., 1994).

The former studies are just a part of greater investigations worldwide, which demonstrate rise in resistance to ciprofloxacin and other kinolones in recent years. The reasons for this dilemma have been enumerated as: massive and inappropriate usage, availability of oral form of ciprofloxacin which makes consumption easier, being low-priced and handy as well (Erfanian et al., 2005). It seems that rise in resistance of gonococci to ciprofloxacin would restrict its application in near future.

In our study 3.8% of gonococci strains showed resistance to ceftriaxone that approximately corresponds to investigation in Mashhad (Erfanian et al., 2005) whilst this figure for Sari was 1% (Nasrolahi, 1999). One of the reasons for this very low rate of resistance maybe limited usage in hospitals as well as intramuscular administration of the drug which is quite painful and gonorrheal victims do not tolerate it easily. Hence, most of global reports have indicated efficacy of ceftriaxone against gonorrhea for instance; all studies in China and Germany have described absolute sensitivity of gonococci strains against ceftriaxone (Zheng et al., 2003; Su et al., 2007; Enders et al., 2006). Other findings in different countries including; Russia, Madagascar, Vietnam and Central Africa have also revealed high sensitivity of strains in question to ceftriaxone (Vorobieva et al., 2007; Cao et al., 2008). Nonetheless, in spite of sensitivity of gonococci to ceftriaxone WHO has strongly recommended antibiogram test before its prescription in order to minimize chances of resistance altogether (WHO, 1999).

In the current study only 2.5% of gonococci strains were resistant to spectinomycin whereas in Sari and Arak this number was 4 and 26%, respectively (Nasrolahi, 1999; Ghaznavi et al., 1999). Interestingly, in China within a span of five years sensitivity to spectinomycin has not change whatsoever and this antibiotic has been introduced as one of the first line of treatment for gonorrhea (Zheng et al., 2003). In the similar studies carried out in Germany and Russia all strains were sensitive to spectinomycin (Enders et al., 2006; Vorobieva et al., 2007) in the same way, findings in Madagascar, Vietnam and Central Africa also indicated high sensitivity of gonococci to spectinomycin (Cao et al., 2008).

Concerning high resistance of gonococci strains against spectinomycin in Iran in comparison to worldwide data and obscurity of this phenomenon, we strongly recommend caution in prescription of this antibiotic as well as proper surveillance of the patient during and after treatment for possible side-effects.

In this investigation, rate of resistance towards cefexim was 12.9% which almost corresponds to study in Mashhad (Erfanian et al., 2005) although, in similar reviews in Germany and Russia all strains were sensitive to cefexim (Enders et al., 2006; Vorobieva et al., 2007). The emergence of this proportion of cefexim-resistant gonococci strains in Iran in comparison with other developed countries is alarming. One of the possible reasons maybe accessibility of oral form of cefexim in the market and patients' self-medication for different infectious diseases regardless of the causative agent.

In accordance with our data in this study, 93.5% of the gonococci strains were resistant against co-trimoxazole although, the latter percentage for Sari was 84% (Nasrolahi et al., 1999) and for Mashhad 92% (Erfanian et al., 2005). Nevertheless, by considering remarkable resistance of the strains in question both in Iran and rest of the world (Ye et al., 2002; Deguchi et al., 2003; Van et al., 2005) it can be claimed that co-trimoxazole is not drug of choice for cure of gonococcal infections.

In this research also, 88.3% of the gonococci strains showed resistance vis-à-vis tetracycline (TRNG) that corresponds with other studies in Iran. For instance; this proportion for Arak, Mashhad, Sari and Kerman was 36, 59, 70 and 73% correspondingly (Ghaznav et al., 1999; Erfanian et al., 2005; Nasrolahi, 1999; Shakibaie et al., 2008). Furthermore, analysis of the data from other countries more or less demonstrates similar figures, for examples in India 18.3% (Khaki et al., 2007) in Germany 29.2% (Enders et al., 2006) and in Russia 92% (Vorobieva et al., 2007) were the percentage of resistance against tetracycline. Surprisingly, in China spread of TRNG strains increased from 1.8% in 1999 to 32.8% in 2006 (Su et al., 2007). In reality, emergence and spread of the plasmids has played an important role amid gonococci resistance against tetracycline worldwide therefore, its

prescription has been restricted since 2000 and is not considered as drug of choice for treatment of gonorrhea as well.

Another antibiotic analyzed in this study was gentamicin that showed 29.8% resistance as a matter of fact, this antibiotic has demonstrated various range of resistance in different investigation in different parts of Iran that varies from 20 to 89% (Ghaznavi et al., 1999; Erfanian et al., 2005; Nasrolahi, 1999). The latter necessitates implementation of sensitivity test before prescription of any antibiotics. Since, gentamicin is not regarded as drug of choice for treatment of gonorrhea thus; we do recommend its exclusion in medication of the so- called infection.

Most of the gonococci strains in our study revealed multi-resistance and could withstand at least three classes of antibiotics totally or partially. Although in comparison with Russian data that showed 72% resistance (Vorobieva et al., 2007) our findings were quite lower, but still alarming.

Our overall findings confirmed that in Zahedan we are facing massive number of gonococci strains which are quite resistant against penicillin, ciprofloxacin, co-trimoxazole and tetracycline. At the same time other antibiotics including; ceftriaxone, spectinomycin and cefexim are absolutely effective for treatment of gonorrhea. Furthermore, resistance due to plasmids' activities has created penicillin and tetracycline ineffective. The latter is because of certain enzymes, which split up antibiotics and such strains are dispersing widely. The authors believe that, lack of detection of minimal inhibitory concentration (MIC) of the antibiotics employed in this survey and absence of other contributory elements in venereal diseases are the main disadvantages of this investigation that will be hopefully dealt with in future studies.

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