

## Penicillinase producing *Neisseria gonorrhoeae* (PPNG) and Tetracycline resistant *Neisseria gonorrhoeae* (TRNG) from Central Kerala

Maria John<sup>1,\*</sup>, Seema Oommen<sup>2</sup>, Abraham Varghese<sup>3</sup>, Sunil Mathew<sup>4</sup>

<sup>1</sup>PG Student, <sup>2</sup>HOD, Dept. of Microbiology, <sup>3</sup>Associate Professor, <sup>4</sup>Assistant Professor, Dept. of Medicine,

**\*Corresponding Author:**

Email: drmariajohn@gmail.com

### Abstract

Gonorrhoea is one of the oldest sexually transmitted disease, which has been mentioned in the Bible and ancient Chinese literature. As per *WHO*, the global incidence of gonorrhoea is 106 million. The incidence of gonorrhoea in Asia is 8.37 million. The incidence of gonorrhoea in many countries is not known due to the suboptimal diagnostics, poor case reporting and lack of surveillance. Reports of gonorrhoea from our country appear to be low, with hardly any documented case from Kerala. Here, we report a 24-year-old male, with a history of exposure, who presented with complaints of pus at the urethral meatus for three weeks duration. On examination; there was muco-purulent discharge from the urethra. The patient was diagnosed as suffering from gonorrhoea by smear and culture. The patient was treated with ceftriaxone 1 gm IV and was discharged in three days. Gonorrhoea usually co-exists with other sexually transmitted diseases like HIV and chlamydial infection. These infections are usually transmitted by an asymptomatic population. The emergence of strains of *Neisseria gonorrhoeae* with decreased susceptibility to cephalosporins and resistance to penicillins, sulfonamides, tetracyclines and recently quinolones and azithromycin is of concern. The speedy rise in treatment failure will give rise to disease progression as in the pre-antibiotic era. To overcome the problem of ongoing drug resistant of *N.gonorrhoeae*, two overlapping goals have to be met: they are public health approach and control of drug resistance which will curtail the spread of these resistant strains.

**Keywords:** PPNG, TRNG, Gonorrhoea, Drug resistance, STI, Urethritis

### Introduction

Gonorrhoea is one of the oldest diseases, which has been mentioned as sexually acquired urethritis in ancient Chinese literature as well as the Bible. According to *WHO*, the global incidence of gonorrhoea is 106 million<sup>(1)</sup> with an equal prevalence with chlamydial infections. In the United States of America in 2012, there were nearly three lakh newly detected cases.<sup>(2)</sup> The incidence of gonorrhoea in Asia is 8.37 million.<sup>(8)</sup> The burden of infection is higher in developing countries than in industrialized countries.<sup>(2)</sup> The incidence of gonorrhoea in many countries are not known due to the suboptimal diagnostics, poor case reporting and lack of surveillance.

Urethral discharge is scanty and mucoid initially, but progresses as profuse and purulent discharge. In males presenting with acute urethral discharge, Gram stain is 97% confirmatory in diagnosing gonorrhoea.<sup>(10)</sup> In females, gonorrhoea manifest as mucosal cervicitis. *Neisseria gonorrhoeae* infects the columnar epithelium of the cervical os and also the Bartholin's glands. Anorectal gonorrhoea is present in 5% of the infected females.<sup>(2)</sup> In the sexually active age group, vagina is lined by stratified squamous epithelium thereby not causing vaginitis. In females a gram stain does not provide a confirmatory diagnosis, hence the sample must always be submitted for culture.

Culture offers a cheap and specific diagnostic test for confirmatory identification. Nucleic acid amplification test can be used in the diagnosis of symptomatic and asymptomatic cases with a high

sensitivity of > 96%.<sup>5</sup> For detecting pharyngeal and rectal infections NAAT is preferred than cultures.<sup>(5)</sup>

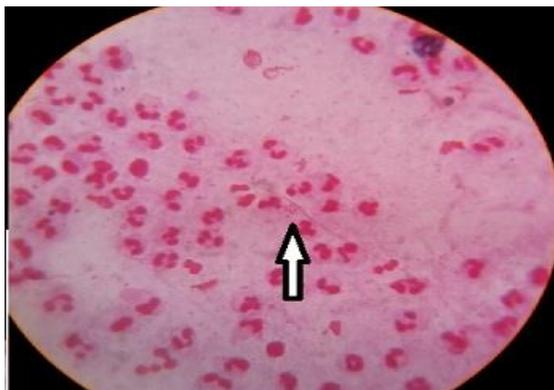
Uncomplicated gonococcal infections of cervix, urethra and pharynx or rectum can be treated with ceftriaxone 250 mg IM single dose, along with azithromycin 1 gm, orally as a single dosage or doxycycline 100mg BD for 7 days for chlamydial infection. In disseminated gonococcal infection, single dose ceftriaxone 1 gm is recommended, as IV or IM. The emergence of strains of *Neisseria gonorrhoeae* with decreased susceptibility to cephalosporins and resistance to penicillins, sulfonamides, tetracyclines and recently quinolones and azithromycin is of concern. The strain which we received showed resistance to penicillin and tetracycline, however it was susceptible to quinolones and cephalosporins. This is the first documented case of PPNG and TRNG reported from Central Kerala.

### Case Report

A 24-year-old male presented with complaints of pus at the urethral meatus for three weeks. The patient works in an airline and is a frequent flier to different parts of the world. He also complained of dysuria and pain at the tip of penis for the last three weeks. He gave history of unprotected heterosexual activity with a Filipino one week prior to the onset of symptoms.

On examination, there was mucopurulent discharge from the urethra. The meatus was cleaned with saline, and the discharge was collected with a swab under sterile, aseptic conditions. A gram stain was prepared, following which it was inoculated on chocolate and

blood agar. It was incubated at 37°C, at 5-10% carbon dioxide for 24 hrs.



**Fig. 1: Intracellular gram negative diplococci**

Gram stain showed large number of pus cells with gram negative diplococci, predominantly intracellular. Chocolate agar showed growth after 48 hrs of incubation. The colonies were small, round, slightly raised, greyish white, opaque with no specific odour. A gram stain was done from the colonies, which showed gram negative diplococci. It was oxidase positive. A superoxol test was done, using 30% hydrogen peroxide which showed effervescence. Sugar fermentation test was done with 1% of glucose, maltose, sucrose and lactose of which only glucose was fermented.

Antimicrobial susceptibility testing was done on GC agar base with 1% defined growth supplement and zone diameters were interpreted using CLSI guidelines.<sup>(4)</sup> The strain was sensitive to levofloxacin, ciprofloxacin, azithromycin and ceftriaxone. It was resistant to penicillin and tetracycline. It was beta-lactamase producer as confirmed with a nitrocefin disc. To rule out other sexually transmitted diseases, HIV (Human immunodeficiency virus) testing and VDRL (Venereal disease research laboratory) testing was done, which came negative. He was asked to repeat test for HIV antibody after three and six months to confirm his HIV antibody status. He was also counseled on safe sex practices.

The patient was treated with ceftriaxone 1 gm IV and he improved with the same and was discharged in three days

## Discussion

Gonorrhoea is caused by non-motile, non-sporing, gram negative diplococci *Neisseria gonorrhoeae* with its adjacent sides flattened, kidney shaped. *Neisseria gonorrhoeae* establishes, its virulence and pathogenicity with the help of outer membrane proteins like pili, opacity associated proteins, porins and lipooligosaccharides. Based on the outer membrane porin proteins, there are two main serotypes, viz: PorB 1A is associated with disseminated gonococcal

infections and PorB 1B is associated with localized genital infections.

Higher proportion of cases has been reported in males, with a male to female ratio of three is to one.<sup>(3)</sup> Males are often symptomatic than females. The predominant age group affected is 15-19 years for females and 20- 24 years in males.<sup>(2)</sup>

The symptoms seen are due to localized inflammation of the mucosa of the genital tract. In men the most common clinical manifestation is acute urethritis with urethral discharge (>80%) and dysuria (>50%), starting within two to eight days of exposure.<sup>(5)</sup> Asymptomatic urethral infection is uncommon in men (< 10%).<sup>(5)</sup> In women >50% of the cases are asymptomatic, if symptomatic the most common manifestations are altered vaginal discharge < 50%, lower abdominal pain < 25% and rarely menorrhagia.<sup>(5)</sup> Transmission of the disease occurs most efficiently from males to females with risk of transmission being 50 % to 70% in a single contact; vertical transmission is also seen in cases of *ophthalmia neonatorum*.

According to WHO in 2008, there is an equal prevalence of Gonorrhoea and Chlamydia, was estimated to be 106 million<sup>1</sup>. Gonorrhoea coexists with other sexually transmitted diseases like HIV. The non-ulcerative inflammatory sexually transmitted diseases like Gonorrhoea, Chlamydia and Trichomoniasis, increases the risk of transmission of HIV. These infections are usually transmitted by asymptomatic population or a population who tends to neglect their symptoms as in the case of commercial sex workers and drug abusers.

The first case of penicillinase producing *N.gonorrhoeae* was confirmed in 1976; it is plasmid mediated and produces TEM-1 betalactamase.<sup>(9)</sup> TRNG or Tetracycline resistant *Neisseria gonorrhoeae* was reported in 1985.<sup>(9)</sup> This is plasmid mediated (tetM), with the formation of a protein coat over the ribosomes which inhibits killing by tetracyclines. This plasmid mediated resistance enables PPNG and TRNG to exist together in the same organism.<sup>(2)</sup> Quinolones were used in treating gonorrhoea, as it gave coverage over chlamydial infections as well. QRNG has developed in Asia and Pacific islands.<sup>(1)</sup> It is also seen commonly in some parts Europe and the Middle Eastern countries.<sup>(1)</sup> Quinolone resistance arises due to alteration in DNA gyrase activity and topoisomerase activity. Third generation cephalosporins has remained effective as a single dose therapy, but recently strains with high resistance to ceftriaxone (MIC 2µg/ml) is emerging.<sup>(2)</sup> In our case, the patient had a penicillinase producing *N. gonorrhoeae* (PPNG) and was also resistant to tetracycline (TRNG) and hence was treated with ceftriaxone 1gm IV.

## Conclusion

The rise in emergence of resistant strains of *N. gonorrhoeae* will lead to treatment failure and disease

progression as in the pre-antibiotic era. To overcome this problem of ongoing drug resistant of *N.gonorrhoeae*, two overlapping goals must be met they are public health approach and control of drug resistance. Public health awareness includes, informing the public of the presence of sexually transmitted diseases in a locality and the need to have protected sexual activity, especially with sex workers. The health care providers should be educated on the correct antibiotic policy. Systematic monitoring of treatment failure, with protocols for verification, reporting and management is also required to contain the spread of these multidrug resistant strains.

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