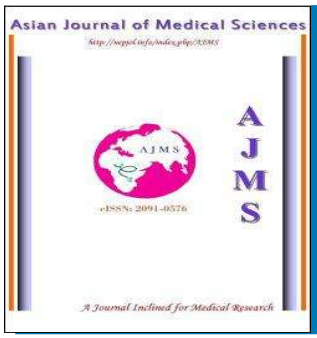

TIME ELAPSED FROM ONSET OF SYMPTOMS TO DIAGNOSIS OF *GONORRHOEA* IN SWEDISH PATIENTS, 1999-2009

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"Significant delay in establishing diagnosis of Gonorrhoea in Swedish patients, 1999-2009."

ABSTRACT

Background: Gonococcal infection remains an important public health problem worldwide. The incidence of reported gonorrhoea cases in Sweden raised by 32%, from 5.9 to 7.8 cases per 100,000 in 2001 to 2008.The aim of this study is to estimate the lag time or time elapsed between onset of symptoms and diagnosis of gonorrhoea, and to identify the factors associated with diagnostic delay in a sample of reported gonorrhoea cases in Sweden.

Methods: A retrospective cohort study was conducted using all reported gonorrhoea cases at the Swedish Institute for Communicable Disease Control (SMI) from the time period 1999-2009. Total number of cases included in final analysis was 2161. Descriptive statistics, ANOVA, independent t-test and multiple linear regression analysis were applied for data analysis.

Results: The mean lag time between onset of symptoms and diagnosis of gonorrhoea was 12.3 ± 18.8 days. There was a significant association of lag time with sex, region, type of clinics and type of specimen and year of diagnosis. In multivariate analysis with adjusted model, type of specimen was found to have independent effect on lag time and there was a significant interaction observed between region and sex indicating difference between sexes was due to difference in regions.

Conclusion: The result of our study revealed a significant delay in establishing a diagnosis in Gonorrhoea patient sample in Sweden. The variables influencing this delay in diagnosis should be addressed to shorten the lag time leading to an early diagnosis and a proper treatment in our patients. However, more research needs to be carried out in this area to better understand the factors at work.

Key Words: Gonorrhoea; Epidemiology; Lag time; Symptoms; Diagnosis; Treatment; Complications.

INTRODUCTION

Gonorrhoea is the second most common bacterial sexually transmitted infection caused by gram negative intracellular diplococci *Neisseria gonorrhoeae*. It has a major impact on health worldwide.[1-3]

Incubation period of gonorrhoea varies from 2-30 days. Infection predominantly involves the columnar epithelium of the urethra, endocervix, rectum, pharynx and conjunctiva. Transmission usually occurred by genital- genital, genital- anorectal, oro-genital or oro-anal contact or by mother-to-child transmission at birth. In women symptoms include increased or altered vaginal discharge, lower abdominal pain, intermenstrual bleeding, dysuria and menorrhagia. In men, the most common complaints are urethral discharge and painful urination (dysuria). Of infected women, 30 to 60 % remain asymptomatic or subclinical whereas only 5-10 % of infected men will not develop symptoms. Rectal and pharyngeal infections are usually asymptomatic. Newborns exposed to infected secretions during birth develop eye infections known as opthalmia neonatorum. [4-5]

Untreated patients remain as carriers for several months leading to ascending and complicated infections and further spread of the disease into the population. Women may suffer from pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy, tubal infertility and adverse outcomes of pregnancy (spontaneous abortion, still birth, prematurity, and a low birth weight of neonate) while men may experience epididymitis, prostatitis and urethral stricture. [2,6] Occasionally, some individuals may also develop disseminated infections with systemic complications. [7-8]

Gonorrhoea infection has also been found to increase susceptibility and transmission of HIV infection.[9-10] Several studies had reported a high proportion of HIV infection in patients with gonorrhoea which suggests that gonorrhoea diagnosis especially in MSM is an important risk marker for HIV.[10]

Gonococcal antibiotic resistance has been increasing for two decades and recently treatment failure have been reported worldwide even with newer therapy such as azithromycin and extended- spectrum cephalosporins such as cefixime and ceftriaxone posing an ongoing problems for the management of individual patients and also at the public health level on disease control effort for gonorrhoea.[11-13]

Globally about 95 million new cases of gonorrhoea were estimated among men and women.[14] In Sweden there was a steady decline in gonorrhoea incidence during the 1970s, 1980s and early 1990s. Similar epidemiological trends were also observed in many other high and middle income countries worldwide.[15] After 1996, the gonorrhoea incidence in Sweden together with other European countries like Denmark, Norway began to rise again.[16-18] Recent study in Sweden has reported about 32 % increment in incidence of gonorrhoea cases over the last eight years (2001 to 2008). Among them up to 86 % of the cases occurred in men with the highest proportion (41-59 %) in heterosexually infected men who acquired infection abroad, mainly in Thailand.[19]

In contrast women and men who have sex with men (MSM) were found to acquire infection within Sweden. This re-emergence of gonorrhoea was primarily due to outbreaks among MSM, increased transmission among young heterosexuals of both sexes and resistance to antimicrobials like penicillin, tetracycline, fluoroquinolones used in the traditional treatment of the gonococcal infection.[11,20] In addition adoption of more risky sexual behaviour for e.g. an increase in the number of sexual partners and the number of new/ casual sexual partners and / or low use of condoms in the Swedish population were also reported as the most likely reason for this recent increase in gonorrhoea cases.[19]

Bearing in mind the increased infection rates, increasing prevalence of antibiotic resistance strains, increased susceptibility to and transmission of HIV infection, and serious complications of gonorrhoea infection, early diagnosis and effective treatment is essential for effective prevention and control of gonorrhoea.[21]

Despite the considerable amount of information published on many different aspects of gonorrhoea, not a single study have evaluated the lag time or time which has elapsed between the onset of symptoms and diagnosis of gonorrhoea. With better knowledge of lag time / diagnosis delay efforts against gonorrhoea

prevention can be more effective.

The aim of this was to estimate the lag time occurring between onset of symptoms and diagnosis of gonorrhoea and to identify the factors associated with lag time in a sample of registered gonorrhoea cases at the Swedish Institute for Communicable Disease Control (SMI) from the period 1999 to 2009.

MATERIALS AND METHODS

This is a retrospective, cohort (of patients) study based on data acquired from the Swedish national computer-based surveillance system 'SmiNet' (www.sminet.se) which is maintained by Swedish Institute for Communicable Disease Control.

In this study, we have included 2161 (32.9 %) cases out of 6555 registered cases at SmiNet in the period between January 1999 and December 2009. Inclusion was based on cases with complete information on date of onset of symptoms and date of diagnosis. We estimated lag time between date of onset of symptoms and date of gonorrhoea diagnosis reported by health-care clinics. Further explanatory variables/ covariates were selected based on their potential influence on lag times to establish diagnosis.

Covariates in our analysis were age, sex, reporting county of Sweden, route of transmission, diagnosis year, types of clinics, types of specimen, type of symptoms and probable continent of acquisition. We compiled reporting county in three different regions: Götaland (GL, southern part of Sweden); Svealand (SL, central part of Sweden) and Norrland (NL, northern part of Sweden). Similarly countries of acquisition were subdivided into six different continents, namely Asia, Africa, South America, North America, Europe and Oceania. We have also used this variable as domestic and abroad acquired cases. Types of clinics were subdivided into Sexually transmitted infection (STI), youth, gynaecological, private and other types of clinics respectively. Types of specimen were also further divided into cervical, rectal, urethral and other type of specimens. Types of symptoms were subdivided into acute symptoms, asymptomatic carrier and other symptoms categories. We categorised age into four different subgroups 0-18, 19-30, 31-42 and >42 respectively.

Statistical analysis:

First of all, descriptive statistics were carried out with mean, standard deviation, frequency, and percent distribution of each variable considered in our analysis. Because of the positive skew for lag time in days, the data were log transformed. Univariate association of lag time with each covariate was assessed using ANOVA and t-tests. Further we conducted multiple regression analysis with log lag time and significant covariates through backward elimination procedure. All the results are reported as mean ± SD unless stated otherwise. For all analyses, a two-tailed approach was used and a p-value less than 0.05 was considered as the level of statistical significance. All statistical analyses were carried out using the statistical software "R- 2.10.1 for WINDOWS" (www.r-project.org).

RESULTS

Description of study sample

Out of 6555 patients only 2161 (32.9 %) with complete information on date of onset of symptoms and diagnosis of Gonorrhoea were included in our study.

The majority of patients were males (92.2 %) and the mean age was 33.4 ± 10.9 (mean ± SD).

The predominant age group was between 19- 30 years (43 %). Among males 43.4% were reported to acquire gonorrhoea through the contact with males and 55.8 % were reported to acquire gonorrhoea through the contact with females. Among female 9.5 % were reported to acquire gonorrhoea through the contact with females and 89.9% were reported to acquire gonorrhoea through the contact with males. Most of the patients in our study were from the central region (Svealand) of Sweden (65.9 %) and the majority of the cases were acquired from Europe (70.5 %). More than half of the cases (58.5%) were found to be infected in Sweden whereas only 38.5 % of cases got infection abroad.

A majority of the patients were having acute symptoms (94.5 %) while presenting at clinic and the commonest route of transmission was heterosexual (57.5 %)

followed by homosexual (40%) and perinatal (0.2 %). Among different types of specimen used for establishing Gonorrhoea diagnosis, urethral discharge was the most predominant (18.5 %) specimen in our study sample.

Most of the patients were diagnosed in STI (Sexually transmitted infection) clinic which accounts for (20.3 %) as compared to youth clinics (1.2%), private (0.7%), gynaecology (0.7 %) and other types of clinics (12.7 %) respectively (Table.1).

Univariate analysis of factors potentially influencing lag times to establish diagnosis and initiate treatment in patients with Gonorrhoea

There was a significant relationship of lag time with sex, region, type of clinics, type of specimen and diagnosis years. But no significant association were detected with age, route of transmission, types of symptoms and probable continent of acquisition (Table 2).

The mean lag time was significantly higher in women than men (16.4 ± 22.8, p< 0.01).

Similarly the mean lag time was found to be longest in northern (13.5 **±** 15.2) part of Sweden and shortest in southern region (10.8 **±** 14.5). We found a significant difference (p < 0.00) in mean lag time between Northern (NL) and Southern (GL) as well as between Central (SL) and Southern (GL) regions of Sweden. Among different types of clinic, the youth clinic had the highest mean lag duration (15.5 **±** 23.7) and STI clinic had the lowest mean lag time (9.4 ± 10.9). There was a significant difference in mean lag time between STI-clinic and other types of clinic (p< 0.00).The mean lag time was highest in case of urethral specimen (14.4 **±** 25.0) and lowest in rectal specimen (8.6 **±** 12.3). There was a significant difference observed between urethral and rectal specimen (p< 0.03). The highest mean lag time was observed in the diagnosis year 2000 – 2004 (13.6 **±** 23.1). There was a significant difference in mean lag time between the diagnosis years 2000-2004 to 2005-2009 (p < 0.01).

Mean lag time was highest in age group 0-18 (15.1 **±** 20.7) and lowest in age group more than 42 years (11.8 ± 15.4). Mean lag time was highest with heterosexual route of transmission (12.4 **±** 16.7) than homosexual (12.3 **±** 21.9) and other route of transmission (7.4 **±** 6.4). Similarly we found that mean lag time was higher in domestic cases (12.6 **±** 21.3) as compared to cases acquired abroad (11.9**±** 12.0). Those patients who probably got infected in Oceania were found to have the longest mean lag time (16.8 **±** 18.0) and cases with probable acquisition in South America had shortest mean lag time (9.5 **±** 6.8). However; these differences were not statistically significant (p >0.05) (Table 2).

Multiple linear regression analyses of lag time with adjusted covariates

In the final model, type of specimen had independent main effect on lag time between onset of symptoms and diagnosis of Gonorrhoea. In addition to it, there was a significant interaction observed between region and sex. We have found that difference between sexes is different in different region. In northern (NL) and central (SL) Sweden, women have longer lag time as compared to men where as in southern (GL) Sweden men have longer lag time than women (Table 3).

DISCUSSION

The mean lag time for all patients included in our study was 12.3 ± 18.8 days which suggests a significant delay from symptoms onset to diagnosis. Further, we detected significant associations of sex, region, type of clinic, type of specimen and diagnosis year with lag time.

To our knowledge, no single previous study has been carried out evaluating lag time between onset of symptoms and diagnosis of gonorrhoea. However there are several studies showing a relation of lag time in other diseases such as rheumatoid arthritis, endometriosis etc.[22-23] Health care disparities, differences in medical care access, patients and physician's lack of awareness of disease, choice of physician or clinic for first consultation, time to carry out diagnostic testing, referral to a relevant specialist, lack of uniform guidelines for diagnosis have been reported to be the cause of potential delay to establish a diagnosis and to initiate treatment in many countries.[22] There might be other various reasons by

Table 1. Descriptive statistics of the sample (N= 2161)

Attributes/ Variables	N (%)
Age (mean ± SD)	33.4 ± 10.9
0-18	66 (3.0)
19-30	931 (43.0)
31-42	753 (34.8)
>42	411 (19.0)
Sex	
Male	1993 (92.2)
Female	168 (7.8)
Region	
NL (Norrland, North)	118(5.4)
SL (Svealand, Central)	1425 (65.9)
GL(Götaland, South)	618 (28.6)
Year of diagnosis	
1999 - <2000	158 (7.3)
2000-2004	1081 (50.0)
2005-2009	922 (42.7)
Lag time in days, mean ± SD	
Lag time between onset of symptoms and diagnosis of Gonorrhoea	12.3 ± 18.8
Log lag time in days, mean ± SD	2.2 ± 0.8
Probable continent of infection	
Asia	478 (22.1)
Africa	47 (2.1)
Europe	1524 (70.5)
South America	12 (0.5)
North America	26 (1.2)
Oceania	7 (0.3)
Missing	67 (3.1)
OR	
Origin of cases	
Sweden	1266 (58.5)
Abroad	833 (38.5)
Missing	62 (2.8)
Type of Clinic	
Private	16 (0.74)
STI	439 (20.31)
Youth	26 (1.20)
Gynae	16 (0.74)
Other	276 (12.77)
Missing	1388 (64.22)
Type of Specimen	
Cervical	29 (1.3)
Rectal	21 (0.9)
Urethral	401 (18.5)
Other	121 (5.6)
Missing	1589 (23.5)
Type of Symptom	
Acute Symptoms	2043 (94.5)
Asymptomatic	9 (0.4)
Other	77 (3.5)
Missing	32 (1.4)
Route of transmission	
Heterosexual	1243 (57.5)
Homosexual	866 (40.0)
Perinatal	6 (0.2)
Other	10 (0.4)
Missing	36 (1.6)

Table 2. Univariate analysis of lag time with age, sex, region, year of diagnosis, probable continent of infection, type of clinic, type of specimen, type of symptoms and route of transmission.

	Lag time	
Variable name / Categories	Mean ± SD	P value
Age (mean ± SD)		
0-18	15.10 ± 20.7	0.72
19-30	12.16 ± 14.4	
31-42	12.67 ± 24.3	
>42	11.85 ± 15.4	
Sex		
Male	16.43 ± 22.8	0.01*
Female	12.03 ± 18.4	
Region		
NL (Norrland, North)	13.54 ± 15.2	0.00*
SL (Svealand, Central)	12.92 ± 20.6	
GL(Götaland, South)	10.89 ± 14.5	
Year of diagnosis		
1999 - <2000	11.46± 12.5	0.01*
2000-2004	13.69 ± 23.1	
2005-2009	10.98 ± 13.1	
Probable continent of infection		
Asia	12.48 ± 11.8	0.18
Africa	13.42± 11.5	
Europe	12.29 ± 20.1	
South America	9.58 ± 6.8	
North America	10.84 ± 8.1	
Oceania	16.85 ± 18.0	
OR		
Origin of cases		
Sweden	12.64 ± 21.3	0.18
Abroad	11.93 ± 12.06	
Type of Clinic		
Private	11.50 ± 3.28	0.00*
STI	9.46 ± 10.9	
Youth	15.57 ± 23.7	
Gynae	12.25 ± 20.3	
Other	11.75 ± 13.1	
Type of Specimen		
Cervical	9.03 ± 8.0	0.03*
Rectal	8.66 ± 12.3	
Urethral	14.48 ± 25.0	
Other	12.48 ± 16.6	
Type of Symptom		
Acute Symptoms	12.40 ± 19.2	0.25
Asymptomatic	9.22 ± 12.9	
Other	12.79 ± 11.4	
Route of transmission		
Heterosexual	12.49 ± 16.7	0.11
Homosexual	12.31 ± 21.9	
Perinatal	12.16 ± 5.07	
Other	7.40 ± 6.4	

* $p<0.05$ is considered as the level of statistical significant

Table 3. Final model of lag-time

	Sum Sq	Df	F value	Pr (>F)
Region	8.34	2	5.66	**0.00 ****
Sex	2.93	1	3.97	**0.04 ***
Type of specimen	7.68	3	3.47	**0.01 ***
Region*Sex	4.93	2	3.34	**0.03 ***
Residuals	**414.86**	**563**		

* p<0.05 is considered as the level of statistical significant, ** p<0.00 is considered as highly statistical significant

which diagnosis may be delayed. Very often symptoms develop insidiously and patients may not seek medical care after several weeks or months of disease onset. It is also likely that the perception of people that it is a desirable character trait to delay seeking help for vague symptoms and wait until they are unquestionably ill. In reality subclinical and asymptomatic infection is not regarded by the patients as sufficiently serious to present to a hospital or clinic. Physicians might miss subclinical infection due to lack of awareness. In many European countries screening for rectal and pharyngeal infections which are often asymptomatic are not included in a routine screening, which might result in under-diagnosis of MSM in particular. [24-26]

We found that women in our study population had significantly higher lag time (16.43 ± 22.8 days) compared to men (12.03 ± 18.4 days). Some studies reported that the average incubation period for women was found to be somewhat longer as compared to male (ten days vs. 2-5 days). Women also reported to be asymptomatic at higher level then men:about 30 to 60 % of infected women will remain asymptomatic or subclinical. However; only 5-10 % of infected men were found to be asymptomatic. Usually most of them have acute symptoms such as urethral discharge and painful urination. [5]

Women has different testing behaviour and are more used to testing as a general screening including Chlamydia test during their routine check up in pregnancy and on visit to gynaecologists and birth control counselling, but they are not routinely tested for gonorrhoea which might be the cause of missing gonorrhoea cases in women. Tested men are more often targeted because of symptoms or through contact tracing. More cases of gonorrhoea are seen in men than women in Europe. Gonococcal infections in women may be under- diagnosed due to the use of suboptimal diagnostic methods which favour the definitive diagnosis of male gonococcal urethritis. [24, 27]

In our study sample majority of the patients were male and among them 43.4 % were reported to acquire infection through the contact with males. Gonorrhoea is often spread through homosexual contacts between men; therefore more men than women were diagnosed early because the risk groups for infection are predominantly men and they are targeted with screening programmes.[7] In Europe including Sweden, Norway Denmark and England, MSM accounts for a disproportionately large burden of gonorrhoea in recent years due to increase unsafe sexual behaviour following the introduction of highly active antiretroviral therapies. [15, 19, 28]

Among different types of clinic, we have found that the mean lag time was longest in patients who presented at youth clinic and shortest in STI clinics. Usually in Sweden, youth clinic deals with younger age group (less than 23 yrs) and patients presented at this clinic are usually not routinely screened for gonorrhoea. This might be one of the reasons in prolonged lag time of gonorrhoea in youth clinics. Same reason could be applied in case of age-group since our result revealed that the youngest age group (0-18) had longest lag time. So general practitioners or physicians have to be aware of gonorrhoea and should not only perform diagnostic samples for Chlamydia alone in these clinics. In addition, timely referral of gonorrhoea cases to STI-clinic is also important for early diagnosis and effective treatment. On the other hand STI clinic serve the population over 18 yrs old and patients presented there might be diagnosed earlier. Therefore mean lag time

might be shortest in patients who presented at STI clinics.

Similarly, we found that urethral specimen had longest lag time while cervical specimen had shortest lag time. This would have been influenced by the type of diagnostic methods used and time to carry out diagnostic testing for gonorrhoea. Microscopy or direct smear for Gram staining can be performed as soon as the specimen is collected and offers a rapid diagnosis within a short time period. However culture needs longer time comparatively for confirmatory identification and antimicrobial susceptibility testing of gonorrhoea.[6] There might be other technical reasons responsible for increased lag time with urethral specimen.

The mean lag time was found to be longest in the diagnosis year 2000-2004. We could not find any specific reason why the lag time was prolonged particularly in these years. However we can speculate that it is more likely due to introduction of new diagnostic tools in order to improve sensitivity and specificity.

CONCLUSION

Our study revealed a significant delay in establishing a diagnosis in a sub-cohort of Gonorrhoea patients in Sweden. The variables influencing this delay in diagnosis should be addressed in order to shorten the lag time leading to an early diagnosis, treatment. Further these findings might help in preventing and control of gonococcal infection.

The findings of our study should guide public health professionals and policy makers in planning an effective and targeted preventive and control strategies towards gonococcal infection. However, more research needs to be carried out in this area to better understand the factors responsible for delayed diagnosis of gonorrhoea in Sweden.

Limitations of the study:

First of all, only one third of the reported cases were included into analysis, which might underestimate or overestimate our results.

Since our study was conducted retrospectively we could not consider some important factors like education, occupation, marital status, sexual behaviour, number of sexual partners,type of diagnostic methods used for gonorrhoea screening that might also be responsible for delayed diagnosis and prolonged lag time.

Data quality in terms of data completeness varied for some variables (e.g. type of doctor or physicians first consulted, reported county of acquisition, type of clinics, type of specimen) and some conclusions need to be drawn with caution.

In addition, the precise date of the onset of symptoms and the date that these symptoms were reported to a physician were totally dependent on the patients' ability to remember facts that very often occurred a long time ago and this may not be absolutely accurate.

Our study sample contained predominantly male patients which is likely to overestimate the effect.

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Authors Contributions:

AS: Concept and Design of the study, analysis and interpretation, manuscript preparation, data collection, statistical analysis, and literature search.

IV: Concept and Design of the study, analysis and interpretation, manuscript preparation, critical revision of the manuscript, statistical analysis, and literature search.

MK: Critical revision of the manuscript and statistical analysis.

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