An epidemiological study of syphilis and predictors of treatment failure in University Malaya Medical Center

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ABSTRACT

Introduction: There are limited studies on the epidemiology of syphilis in Malaysia. In this study we describe the clinical features and treatment outcomes of patients with syphilis attending a tertiary referral university hospital.

Methods: We retrospectively reviewed the case records of patients with positive serology findings for syphilis in University Malaya Medical Center (UMMC) from January 2010 to December 2015. Serological positivity was defined as having a positive rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) with a confirmatory positive *Treponema pallidum* particle agglutination assay (TPPA). Treatment outcomes were divided into two, success or failure. Demographic and clinical characteristics associated with predictors of treatment failure were assessed using statistical package for the social science (SPSS). This study also included a neurosyphilis descriptive sub-study.

Results: There were 637 patients identified with positive syphilis serology, but 258 patients were excluded as they did not meet the inclusion criteria. 379 patients were then taken for the demographic study; 14 patients (3.7%) were treated for neurosyphilis; 170 patients with complete data were included. In all 42/170 (24.7%) failed treatment, 12/170 (7.1%) had reinfection and 116/170 (68.2%) had treatment success. A final number of 158 patients were then taken and analyzed for predictors of treatment failure after excluding the 12 re-infection patients. Only low baseline RPR (<1:16) was found to be significant on multivariate logistic regression analysis (p value: 0.007, 95% CI: 1.42, 9.21).

Conclusion: Most of the patients were HIV positive and from the MSM (Men who have sex with Men) population. Low baseline RPR titre is a predictor of treatment failure.

KEY WORDS:
Syphilis serology, predictors, treatment failure, titre

INTRODUCTION

Syphilis is a sexually transmitted disease caused by *Treponema pallidum*.[1] In many parts of the world the incidence of syphilis has increased especially among the human immunodeficiency virus (HIV) infected population.[2] It is especially more prevalent in men who have sex with men (MSM). In 2010 World Health Organization (WHO) estimated that 11 million new syphilis infections. The incidence of syphilis was initially low during the 1980s and 1990s in the United States of America and noted to rise during the end of 1990's.[4] In many parts of Asia too, especially in China and Thailand, syphilis infections had risen steadily.[2] Ministry of Health of China even created a national programme to combat syphilis, the National Program for Prevention and Control of Syphilis in China (2010-2020). This programme was created to combat and eradicate syphilis by screening and treating high risk patients (MSM, sex workers, individuals with multiple sex partners and immigrants). However, the incidence actually increased in-spite of this national intervention. Episodic outbreaks of syphilis is common in many parts of the world.

Several studies have demonstrated that some factors such as baseline rapid plasma reagin (RPR), stages of syphilis, concomitant HIV infection are predictors in determining treatment failure.[5] For example, Ghanaem et al. found that CD4 cell count of <200 cells/ml and the lack of antiretroviral therapy was associated with treatment failure.[6] Previous studies also had shown that the treatment outcomes differ in HIV positive and HIV negative patients. In this study, we have looked into this predictors (e.g. stages of syphilis, treatment regimens, baseline RPR and presence of symptoms) in determining treatment failure both in HIV positive and HIV negative patients. This is relevant especially for the treating physician to be vigilant in predicting the high risk patients (who may fail treatment) and hence to prevent syphilis from further being transmitted sexually.

To date there is no accurate data pertaining to the incidence of syphilis in Malaysia due to low notification rates. Hence this study was undertaken to show the burden of syphilis here. This study also included a neurosyphilis descriptive sub study which examined the indications for lumbar puncture in patients with positive serology and the criteria used by the physician to guide treatment.

The primary objective of the study was to describe the epidemiology and clinical features of patients with syphilis infection in UMMC. The secondary objective was to assess predictors of treatment failure.

MATERIALS AND METHODS

We conducted a retrospective record review of all the patients with syphilis. Case records of all patients with a positive

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syphilis serology who attended the infectious diseases ward and the infectious diseases outpatient clinic in University Malaya Medical Center (UMMC) from January 2010 till December 2015 were examined. This data was obtained from the microbiology laboratory of UMMC.

The inclusion criteria were as follows: (1) positive syphilis serology as defined by positive RPR or positive venereal disease research laboratory (VDRL) with confirmatory *Treponema pallidum* particle agglutination (TPPA) or negative RPR or negative VDRL with confirmatory TPPA. (2) Patients were required to have at least 6 months serological follow up after treatment.

The exclusion criteria were: (1) those patients who were treated for syndromic management of syphilis without serological confirmation; (2) those without documentation of treatment; (3) those weakly positive RPR with repeatedly negative TPPA; (4) those with less than 6 months serological follow up post treatment; and (5) those with congenital syphilis.

For those patients who satisfied the inclusion criteria, medical case notes from the medical records unit were reviewed to obtain information on their demographics. The variables obtained were age, gender, race, risk group, HIV status including the CD4 cell counts and viral load, stages of syphilis, symptoms, baseline RPR titer, treatment history, history of other sexually transmitted infections (STI), sexual history and partner notification. Risk group was further divided into MSM, heterosexual, bisexual and neurosyphilis. CD4 cell counts, HIV viral load, highly active antiretroviral therapy (HAART) and symptoms were evaluated as a dichotomous variable (CD4 cell count <350 cells/ml or >350 cells/ml, HIV viral load as detectable or undetectable, presence or absence of HAART and whether patients was symptomatic or asymptomatic). Baseline RPR titres were divided into titres of <1:16, 1:16-1:64 and >1:64. Stages of syphilis were: the early syphilis which is the primary, secondary and early latent syphilis and the late syphilis which is late latent syphilis and neurosyphilis.7 Stages were further classified according to the clinical features and duration of the infection. Primary syphilis is the presence of anogenital or oropharyngeal ulcer.[7] Secondary syphilis is rash involving bilateral palms and soles, but can also appear in other areas of the body.[7] Early latent syphilis was defined as newly positive syphilis serology within the past 2 years and no clinical signs of syphilis.[7] Late latent syphilis was of unknown duration with no clinical signs.[7]

Neurosyphilis was diagnosed with positive syphilis serology with the presence of neurological symptoms, or raised cerebrospinal fluid (CSF) white cell count >20 cells if HIV positive and CSF white cell count > 5 cells if HIV negative and positive CSF VDRL obtained via lumbar puncture (LP).7 Indications for LP includes presence of neurological symptoms, low CD4 count, high RPR titres (>1:32) and lack of 4 fold decrease in RPR titre.[7,9]

Syphilis was treated with Penicillin. In the case of primary or secondary syphilis it was treated with Benzathine Penicillin G 2.4 MU intramuscularly (IM) in a single dose. In late latent syphilis or syphilis of unknown duration it was treated with IM Benzathine Penicillin G 7.2 MU in total, administered as 3 doses of 2.4 MU each at 1 week interval. In patients with penicillin allergy, T. Doxycycline 100mg BD for 14 days or T. Azithromycin 2g stat dose.7 Neurosyphilis was treated with aqueous crystalline penicillin G 18 – 24 million units per day, administered as 3 – 4 million units IV every 4 hours or continuous infusion, for 10 – 14 days.

To identify potential predictors of developing treatment failure, we compared demographic and clinical characteristics of patients with treatment success and treatment failure using simple logistic regression. Risk factors which was found significant on simple logistic regression analysis was then selected for stepwise algorithm in the multivariate logistic regression. A multivariate logistic regression using Omnibus test of model coefficients and Hosmer and Lemeshow test was then calculated. Data were analyzed using statistical package for social science (SPSS) version 20.0. A p value <0.05 was taken as statistically significant.

One of the objectives of this study was to assess predictors of treatment failure. Syphilis treatment outcome were divided into treatment success, treatment failure and reinfection. Treatment success was defined as a 4 fold decrease in non-treponemal (RPR) titres at or beyond 12 months for primary and secondary syphilis and at or beyond 24 months for late latent syphilis.[7] Treatment failure was defined as a 4 fold increase in non-treponemal (RPR) titres or a lack of 4 fold decline in RPR titres at or beyond 12 months for primary and secondary syphilis and at or beyond 24 months for late latent syphilis.[7] Treatment re-infection was defined as a 4 fold increase in RPR titres after treatment, supported by a documented history of having unprotected sex with a potentially infected person.[7] This treatment outcome definitions are as per Center for Disease Control (CDC) guidelines. In the predictors of treatment failure analysis, patients who did not have post treatment RPR titres of less than 12 months in early syphilis, patients who did not have post treatment RPR titres of less than 24 months in late latent syphilis and patients with re-infection were excluded from this analysis.

RESULTS

During the study period, a total of 637 patients with positive syphilis serology were identified. Among the 637 patients, 258 patients were excluded on the basis of having no baseline RPR titre, those who were lost to follow up or follow up period of less than 6 months. In all 379 patients were then included and of them 359 patients were males (94.7%). Most were Chinese (n=211, 55.8%). 73.4% were MSM. Out of 379 patients, 295 patients were HIV positive (77.8%). A total of 105 patients of 295 patients were newly diagnosed HIV positive. Of the 295 HIV positive patients, 129 patients (43.7%) had CD4 cell count <350 cells/ml. The mean CD4 cell count was 289 cells/ml. 104 patients out of the 295 HIV positive patients had undetectable viral load (35.2%). The mean viral load was 2.194 copies/ml. 179 patients with HIV positive (60.7%) were on HAART. 305 out of 379 patients (80.5%) were asymptomatic. A total of 74 patients were

Table I: A simple logistic regression analysis of Clinical characteristics and predictors of treatment failure among 158 patients with syphilis

Clinical Characteristics	Patients with Treatment success (n= 113)	Patients with Treatment failure (n= 45)	p value
Gender			
Gender	110 (97.3)	41 (91.1)	8 (17.8)
Male	3 (2.7)	4 (8.9)	
Female			
Race			
Malay	34 (30.1)	19 (42.2)	0.53
Chinese	59 (52.2)	22 (49.0)	
Indian	10 (8.9)	2 (4.4)	
Others	6 (5.3)	1 (2.2)	
Foreigners	4 (3.5)	1 (2.2)	
HIV			
Positive	88 (71.5)	25 (71.4)	0.98
Negative	35 (28.5)	10 (28.6)	
HAART			
Yes	52 (59.1)	24 (68.6)	0.33
No	36 (40.9)	11 (31.4)	
CD4 cell count (cells/ml)			
<350	45 (51.1)	16 (45.7)	0.59
>350	43 (48.9)	19 (54.3)	
Symptoms			
Asymptomatic	66 (58.4)	35 (77.8)	0.02
Symptomatic	47 (41.6)	10 (22.2)	
Baseline RPR titre			
< 1:16	43 (38.1)	30 (66.7)	0.002
1:16- 1:64	25 (22.1)	7 (15.6)	0.495
> 1:64	45 (39.8)	8 (17.8)	
Treatment history			
T. Doxycycline 100mg BD	4 (3.6)	0 (0.0)	0.649
IM Benzathine Penicillin x 3	78 (69.0)		0.02
IM Benzathine Penicillin x 1	17 (15.0)		
IV C Penicillin x 2/52	14 (12.4)		0.27
Stages			
Late Latent	65 (57.5)	36 (80.0)	0.108
Neurosyphilis	14 (12.4)	0 (0.0)	
Primary	6 (5.3)	1 (2.2)	
Secondary	28 (23.3)	8 (17.8)	

Table II: A multiple logistic regression analysis of clinical characteristics and predictors of treatment failure among 158 patients with syphilis

Clinical Characteristics	OR	95% CI	p value
Baseline RPR			
< 1:16	3.615	1.42, 9.21	0.007
1:16- 1:64	1.4	0.44, 4.54	0.55
> 1:641			

OR: odds ratio; CI: confidence interval, 1reference group

symptomatic. Symptoms included genital ulcer (n=12), maculopapular rash (n=49) and neurological symptoms (n=14). Late latent syphilis was the predominant stage (n=305, 80.5%). IM Benzathine Penicillin x 3 was the predominant treatment regimen used, (n=317, 83.6%).

Other variables assessed were those associated sexually transmitted infections. The most common was genital warts (n= 16, 4.2%), gonorrhea (n=6, 1.6%) and herpes simplex infection (n=5, 1.3%). Anal and oral sex constitutes the most common mode of sexual transmission (n=76, 20.1%) followed by anal sex (n=42, 11.1%) and vaginal sex (n=38, 10.0%).

Of the 379 patients with syphilis, the syphilis status of only 52 of their partners were known. The study also included a neurosyphilis descriptive sub study. A total of 72 patients were counselled for a lumbar puncture (LP). 5 patients refused LP. 67 patients had an LP. The most common indications for LP were presence of neurogical symptoms (n=17), low CD4 count (n=16), high RPR titre (n=12) and lack of 4 fold decrease in RPR titre (n=8) or a combination of either one. Of the 67 patients who underwent LP, 14 patients were treated as neurosyphilis. 9 patients had neurological symptoms, 4 patients had positive CSF VDRL and 1 patient had raised CSF white cell count. These 14 patients were treated with IV C penicillin 2.4MU QID x 2/52 and had treatment success. This is evidenced by a 4 fold decrease in

pretreatment RPR titre at or beyond 24 months and resolution of clinical symptoms. All 14 patients are HIV positive.

For the purpose of treatment outcome statistical analysis, of the 379 patients with syphilis, 209 patients were then excluded. This is because of no 12 month follow up RPR titre for early syphilis and no 24 month follow up RPR titre for late latent syphilis. Of the total 170 patients then, 42 patients (24.7%) had treatment failure, 112 patients (68.2%) had treatment success and 12 patients (7.1%) had re-infection. A total of 158 patients were then analyzed in the univariate analysis after excluding patients with re-infection. Based on the 158 patients, 42 patients (26.6%) had treatment failure and 116 patients (73.4%) had treatment success. By simple logistic regression analysis, certain risk factors were identified as predictors of treatment failure such as low baseline RPR titre; <1:16 (p = 0.002), treatment history with T. Doxycycline (p = 0.05) and asymptomatic patients (p= 0.02).

Using a p value cutoff of < 0.05, a multiple logistic regression demonstrated that predictors of treatment failure in patients with syphilis is low baseline RPR (<1:16). Baseline RPR of >1:64 was taken as the reference group.

Patients with lower baseline RPR (<1:16) had 4 times (95%CI: 1.42, 9.21) were more likely to fail treatment as compared with patients with baseline RPR > 1:64 which is the reference group.

DISCUSSION

Our study is a retrospective record review which shows the epidemiology of syphilis in a Malaysian tertiary center (UMMC). Globally the incidence of syphilis is increasing. In many parts of Asia, studies especially among the MSM and transgender women have noted that the incidence of syphilis is rising.[9,10] This study also reflects a similar findings where the majority of patients were young MSM. MSM is a high risk population which is of public health importance in preventing STI and HIV worldwide. A recent study in Thailand, the Bangkok MSM cohort showed this trend is on the rise and is of great concern now and concludes that STI screening be made routine investigations.[11] The incidence of syphilis is seen to increase if there is concomitant HIV infection. Many studies have shown that concomitant HIV infection facilitates transmission of STI's and vice versa.[12] A total of 78% of our patients were HIV positive. The pathogenesis of transmission of this organism might be related to impairment of cell mediated and humoral immunity in HIV. This thus alters the defense mechanisms of host against the syphilis organism and facilitates the spread of *T.pallidum*. Syphilis also facilitates HIV infection by up-regulating the gene expression.[12] Presence of a sore or ulcer can also facilitate the transmission of the HIV virus especially during sexual acts without condoms. Ulceration and cutaneous lesions worsened during concurrent HIV and syphilis infection. Patients might even present with uncommon clinical features.[13] Thus screening for syphilis is important especially among the newly diagnosed HIV positive patients to prevent further transmission.

This study also showed that the low numbers of partner notifications. Studies done showed the rate of partner notification is still low in many countries.[14] Partner notification is an important public health tool in controlling STI.[14] It has been shown that partner notification had led to many undiagnosed syphilis and new HIV infections. Timely notification and treatment of partners infected with STD is important to prevent further transmission and re-infection rates. The low rates of partner notification in our study is of great concern. Hence doctors need to emphasize more on partner notification. Partner notification should be made compulsory especially in dealing with STIs.

Another characteristic which was initially found significant on simple logistic analysis was the absence of symptoms and treatment failure with T. Doxycycline 100 mg BD compared with IM Benzathine Penicillin x 3. Many studies done showed favorable outcomes with IM Benzathine Penicillin x 3.[15] The mainstay of treatment for syphilis traditionally is Penicillin. Lately oral Doxycycline and oral Azithromycin has been used as an alternative to Penicillin for syphilis treatment especially in primary and secondary syphilis. Treatment failure due to doxycycline resistance is possible. This can be due to ribosomal protein mutation or enzymatic inactivation of the antibiotic. Noncompliance to doxycycline may also lead to treatment failure as doxycycline is taken twice a day and causes gastrointestinal side effects.[16]

Asymptomatic patients presents as late latent syphilis. One of the characteristics of late latent syphilis is the duration of syphilis is unknown. Patients often have a longer duration of infection and thus the treatment response may be poorer in those who have established infection for a longer time. The longer the duration of infection, the lower the metabolic activity of the syphilis infection and hence longer duration of clearance of the *T.pallidum*.[17]

Early syphilis show better serological response compared to late latent syphilis.[17] We did not however find a significant association between syphilis stages and treatment response in our study.

There are studies done to show predictors of treatment failure. For example, Jinno et al predicted that baseline RPR titre <1:16, syphilis history and CD4 cell count <350 cells/ml should be closely monitored for treatment failure post syphilis treatment.5 In our study we found that the lower the baseline RPR (<1:16), the greater the likelihood of treatment failure. This is consistent with some recent studies done.[5,18] Patients with higher RPR titres are likely to be able to mount a more robust immunological response following treatment which is associated with faster and better clearance of organisms from the body. Patients with lower titres of RPR may also have a longer duration of infection and the response to the treatment given may be delayed and longer as the organisms will take a longer time to clear out from the body. Another theory is that patients with higher RPR titres would be simply easier to have a 4 fold decrease in pretreatment RPR titre compared to the one's with lower pretreatment RPR titre.[19]

This study also showed that there were 14 patients who were all HIV positive patients treated for neurosyphilis of the 67 patients who underwent LP. In view of small number of patients with neurosyphilis, analysis was not done. *T.pallidum* can invade the central nervous system early and causes a range of symptoms from headache initially to ocular syphilis, meningovascular syphilis and tabes dorsalis. This can be related to the immunosuppression from the HIV infection facilitating transmission of *T.pallidum* across the central nervous system. Certain studies indicated that there is a direct relation between CD4 count and viral load in predicting neurosyphilis. In this study we found that the main indicator for doing an LP to diagnose neurosyphilis was presence of neurological symptoms with low CD4 count <200 cells/ml, high RPR titre (>1:32) and lack of 4 fold decline in post treatment RPR titre. This is as per the latest guidelines.[7]

This study has several limitations. Since it is a retrospective record review only case records were reviewed. Some of the data was not properly documented and hence could not be included especially sexual history and partner notification and may lead to bias. The other limitation also includes the significant number of patients who had to be excluded from the treatment outcome analysis as they had inadequate RPR follow up. We took a one time point which is 12 month for early syphilis and 24 month for late latent syphilis. This is as per the latest Center for Disease Control (CDC) guidelines. This is probably because of clinical resolution of symptoms, cost factor and patient non-compliance which may have led to less accurate assessment of the treatment outcomes. Ideally the follow up RPR should be at 3, 6, 12 and 24 months until the RPR is negative. Since this is a retrospective review of the medical records, it is likely to be incomplete. The other limitation of the study is the misclassification of the stages of syphilis.

The strengths of the study is the number of patients especially for the demographic analysis. The other strength is that this is possibly the first epidemiological study of syphilis and predictors of treatment failure study in a Malaysian tertiary center.

CONCLUSION

Syphilis is a public health burden. Incidence of syphilis is high in Malaysia especially among MSM population. In our study we found that most of the patients were HIV positive and asymptomatic.

Low baseline RPR (<1:16) is a predictor of treatment failure in syphilis. Hence these patients should be monitored closely for treatment failure.

ETHICAL APPROVAL

This study was approved by the Medical Ethics Committee of University Malaya Medical Center (MECID. NO.: 20161-2048).

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