Syphilis: Prevalence in a Hospital in Lisbon

Sífilis: Prevalência num Hospital de Lisboa

Leonor LOPES✉[1], Rita FERRO-RODRIGUES[2], Samuel LLOBET[3], Luís LITO[3], João BORGES-COSTA[1,4,5]
Acta Med Port 2016 Jan;29(1):52-55

ABSTRACT

Introduction: Syphilis is a sexual and vertical transmitted disease. Its incidence is increasing in Europe, particularly, in Portugal.

Material and Methods: A descriptive, retrospective study was performed based on positive treponemal tests from January to December 2013, at the Santa Maria Hospital, Lisbon. In-patients and out-patients evaluated in medical appointments and at the emergency department were included. We proceeded to epidemiological characterization, disease classification and definition of risk factors.

Results: We obtained a sample of 580 patients, of whom 51 with no clinical data and 45 with false positive serologies were excluded. There was a predominance of male patients (75%) and a mean age of 47 years. Most (59%) had syphilis successfully treated in the past and 3.7% were in follow-up. We recorded 13 primaries syphilis, 71 cases of secondary syphilis, 40 cases of early latent syphilis, 49 unknown duration syphilis and five cases of late latent syphilis. In the early syphilis group, 42% (n = 124) were HIV-positive and, in 8% both diagnosis were done simultaneously.

Discussion: We emphasize the high prevalence of syphilis/HIV co-infection in patients with early syphilis, reinforcing the importance of promoting the use of preventive measures. We obtained 11% of patients with late clinical forms, which are notifiable since June 2014, in Portugal. All serological tests for the diagnosis of syphilis have limitations which emphasizes the importance of clinical-laboratory correlation.

Conclusion: Syphilis remains an important public health problem. It is necessary to establish education programs, screening and follow-up strategies to reduce their prevalence and to perform more efficient screening of the partners.

Keywords: Portugal; Syphilis/epidemiology.

RESUMO

Introdução: A sífilis é uma doença de transmissão sexual e vertical. A sua incidência está a aumentar na Europa, particularmente em Portugal.

Material e Métodos: Estudo retrospetivo baseado na análise laboratorial de testes treponémicos positivos, entre janeiro e dezembro de 2013, no Hospital de Santa Maria. Foram incluídos doentes internados, da consulta externa, do hospital dia e da urgência. Procedeu-se a caraterização epidemiológica, classificação da doença e de fatores de risco associados.

Resultados: Obteve-se uma amostra de 484 doentes, após exclusão de 51 por ausência de dados clínicos nos processos e de 45 por valores falsos positivos. Verificou-se predomínio do sexo masculino (75%) e idade média de 47 anos. A maioria (59%) tinha testes serológicos compatíveis com sífilis no passado e 3,7% encontrava-se em vigilância clínica. Diagnosticou-se sífilis primária em 13 doentes, secundária em 71, latente precoce em 40, latente indeterminada em 49 e latente tardia em cinco. No grupo sífilis recente, 42% (n = 124) eram seropositivos para o VIH e 8% tiveram, em simultâneo, este diagnóstico.

Discussão: Salienta-se a elevada prevalência da coinfeção pelo VIH nos doentes com sífilis recente, reforçando a importância de promover a utilização de medidas preventivas. Registaram-se 11% de formas clínicas tardias, que são de notificação obrigatória desde junho de 2014. Todos os testes serológicos para o diagnóstico de sífilis apresentam limitações, o que enfatiza a importância da correlação clínico-laboratorial.

Conclusão: A sífilis continua a ser um problema de saúde pública pelo que é necessário estabelecer programas de educação, rastreio e follow-up para reduzir a sua prevalência e tornar mais eficiente o rastreio dos parceiros.

Palavras-chave: Portugal; Sífilis/epidemiologia.

INTRODUCTION

Syphilis is a sexually or vertically-transmitted infectious disease caused by the spirochete *Treponema pallidum pallidum*. Clinical features are polymorphic and include genital ulcers, skin rashes, swollen lymph nodes, cardiovascular and neurological involvement, with a significant morbidity, mainly regarding maternal and foetal health. Clinical diagnosis requires non-treponemal and treponemal confirmatory tests. Laboratory diagnosis of primary syphilis may also be obtained by dark-field microscopic or by polymerase chain reaction (PCR) demonstration of the treponema upon examination of exudate obtained from lesions.

Syphilis overall statistics show around 10 million new patients each year.[1] There is an increasing incidence in Europe,[2] particularly in MSM (men who have sex with men) community. Only early or primary syphilis was notifiable in Portugal until 2013 and, according to the *Direção Geral de Saúde*, an increased incidence has been found between 2011 and 2012.[3] The prevalence of other stages of syphilis is unknown and notification does not include any other important data such as co-infections.

1. Serviço de Dermatologia. Hospital de Santa Maria. Centro Hospitalar Lisboa Norte. Lisboa. Portugal.
2. Serviço de Infeciologia. Hospital de Santa Maria. Centro Hospitalar Lisboa Norte. Lisboa. Portugal.
3. Serviço de Patologia Clínica. Hospital de Santa Maria. Centro Hospitalar Lisboa Norte. Lisboa. Portugal.
4. Unidade de Investigação em Dermatologia. Instituto de Medicina Molecular. Faculdade de Medicina. Universidade de Lisboa. Lisboa. Portugal.
5. Departamento de Microbiologia Médica. Instituto de Higiene e Medicina Tropical. Lisboa. Portugal.
✉ Autor correspondente: Leonor Lopes. leonorlopes@gmail.com
Recebido: 27 de janeiro de 2015 - Aceite: 03 de agosto de 2015 | Copyright © Ordem dos Médicos 2016

Our study aimed to identify the number of patients presenting with syphilis at a Lisbon-area tertiary public hospital, as well as classifying the different stages and analysing associated laboratory and demographic variables.

MATERIAL AND METHODS

This was a retrospective and descriptive study on the laboratory analysis of treponemal and non-treponemal tests carried out between 1 Jan and 31 Dec 2013 at the *Hospital de Santa Maria*, in Lisbon. There is currently no universal screening program in this hospital and tests are only obtained when requested by physicians. However, the same diagnosis algorithm is always followed. An epidemiological characterisation was obtained, including patient's gender, age and place of diagnosis, clinical and associated risk factor classification (history of syphilis or any other sexually transmitted disease [STD]). Inclusion criteria were established and included patients at least 16 years of age and with at least one positive treponemal test [CLIA (chemiluminescence immunoassay) and/or TPHA (Treponema pallidum haemagglutination)] in patients attending to outpatient, emergency and inpatient departments. Our study was approved by the Ethics Committee on the 13 Nov 2013. The CDC (Centers for Disease Control and Prevention) criteria for the classification of stages of syphilis were followed, as shown in Table 1.

RESULTS

In total, 8,637 treponemal tests were carried out at the *Hospital de Santa Maria* in 2013 and, from these, 580 patients (initial sample) met the inclusion criteria and 51 patients were excluded from the study due to lack of clinical data allowing for the classification of stages of syphilis and 45 due to false positive tests [positive CLIA; negative TPHA and fluorescent treponemal antibody absorption (FTA-abs) tests)] (Fig. 1).

The final group included 484 patients (363 male), aged between 16 and 86, with 46.6 ± 14.7 average age (in years).

As regards the stages of syphilis, most patients (n = 288) had serology tests consistent with previously treated syphilis and 3.7% of the patients were still followed up as diagnosis had been obtained by the end of 2012 and with VDRL titres ≥ 1:2. In total, 124 patients with early syphilis were identified. Clinical classification of the patients with early syphilis is shown in Table 2.

Late syphilis was observed in 54 patients, from which 49 with latent syphilis of unknown duration and 5 with late latent syphilis. Eight patients had secondary syphilis with CNS (central nervous system) involvement (three patients with meningovascular and two with ocular syphilis and one with syphilitic otitis). No patient with tertiary syphilis was found.

In the group of patients with early syphilis, 42% (n = 52) had personal history of HIV infection, already followed as outpatients and 33% (n = 41) had personal history of syphilis. Ten new cases of syphilis/HIV coinfection (8%) were found. The other STDs found included: human papillomavirus infection (n = 5), hepatitis C virus infection (n = 3), genital herpes (n = 3), *Chlamydia trachomatis* (n = 3) and *Neisseria gonorrhoeae* (n = 1) infection. In the group of patients with recent neurosyphilis and secondary syphilis 27 patients had personal history of HIV and eight patients were initially diagnosed with syphilis.

Positive tests regarding 73 patients were requested in Emergency, regarding 127 patients in outpatient and regarding 284 inpatients (0.7% of total admissions). Inpatients mainly derived from Medicine and Infectious Diseases Departments and outpatients from Infectious Diseases Day-Care Unit and from Dermatology Outpatient Clinic. As regards the patients with primary and secondary syphilis, 61 patients derived from Emergency, 10 patients both from Dermatology and Infectious Diseases Outpatient clinics and the remaining three patients from other Departments.

Table 1 – Stages of syphilis

Stages	Definition
Primary syphilis	Presence of at least one ulcer consistent with the diagnosis and one reactive serologic test (VDRL or RPR, FTA-abs or MHA-TP).
Secondary syphilis	Localized or diffuse mucocutaneous lesions frequently associated to generalised lymphadenopathy. The primary chancre may still exist. Reactive treponemal and non-treponemal tests (VDRL or RPR with titre ≥ 4) are required.
Early latent syphilis	When infection occurred during the year preceding patient's evaluation and at least one of the following criteria: Documented seroconversion or fourfold or greater increase in titre of a non-treponemal test; unequivocal symptoms of primary or secondary syphilis over this period of time; sexual exposure to a partner with early syphilis during this stage; positive non-treponemal or treponemal tests whose only possible exposure occurred during the previous 12 months.
Late latent syphilis	When infection occurred more than 12 months before and does not comply with specific criteria for early latent syphilis. Reactive treponemal and non-treponemal tests required.
Latent syphilis of unknown duration	Does not meet early nor late latent syphilis criteria; with reactive treponemal and non-treponemal tests.

MHA-TP: microhemagglutination assay for antibodies to *T. pallidum*

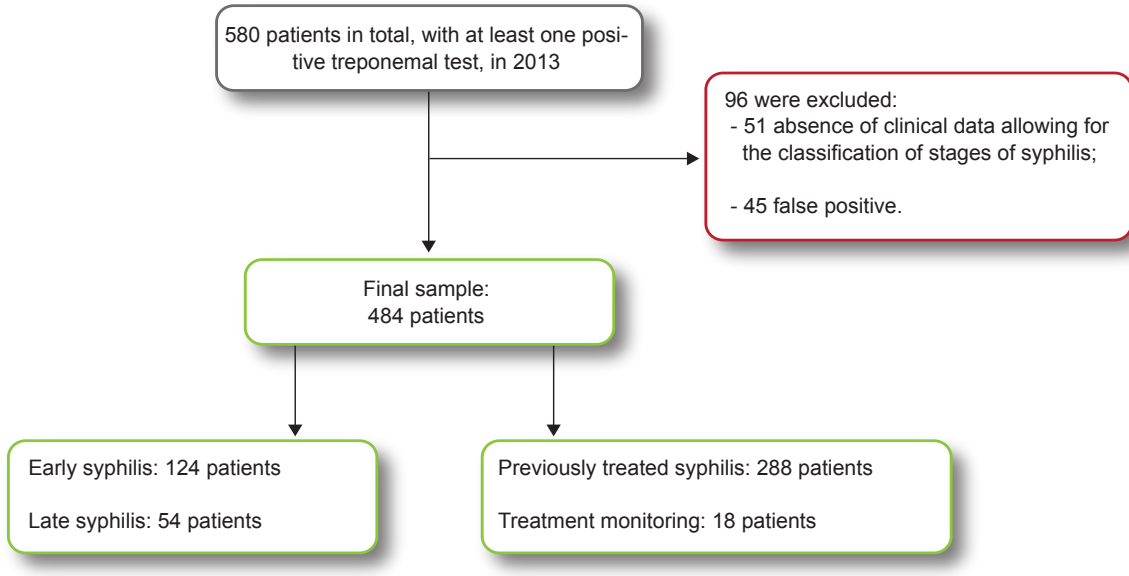

Figure 1 – Study fluxogram

Seven patients presented with discrepant treponemal test results (positive CLIA and negative TPHA). From these, five had personal history of syphilis and HIV infection. As regards stating, previously treated infection (n = 4), early latent syphilis (n = 2) and latent syphilis of unknown duration (n= 1) were found. No patients with positive TPHA and negative CLIA tests were found (Table 3). CLIA was not obtained for 90 patients. Prozone phenomenon (false negative response resulting from high antibody titres) was found in seven patients.

DISCUSSION

Syphilis, as well as other genital ulcer diseases, act as a potent facilitator of HIV transmission, disrupting the protective epithelial/mucosal barrier and producing local inflammation.[4,5] In addition, the activation of the immune response in infected hosts contributes to an increased viral replication.[5,6] Syphilis/HIV coinfection is quite common in MSM, with between 49 and 75% prevalence.[5]

High percentages of recently acquired syphilis infection in HIV-infected patients (70.4%) as well as other STDs (31.5%) were found in Portugal by Ferreira *et al.*[7] A 50% percentage was found in patients with early syphilis in our study. Such high rates are associated to persistent sexual risk behaviours as well as to non-compliance with preventive measures regarding the transmission of STDs. Therefore, laboratory screening targeted at risk populations is recommended (drug users, multiple sexual partners, HIV and MSM) annually or whenever clinically appropriate. A screening of other DSTs should also be carried out in these patients, namely HIV, HBV and HCV infection blood screening, PCR determination of *Chlamydia trachomatis* in urine and *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in urethral exudates.

STD screening is not systematically carried out by all physicians, explaining for the small number of patients identified in our study. Apart from the lack of a uniform screening protocol, the lack of data in patients' clinical records was one of the major limitations to our study, leading to the exclusion of 51 patients and the unavailability of relevant variables for STD control programs, such as patient's sexual orientation, ethnicity, number of sexual partners and consistent use of barrier methods during sexual activity.

European guidelines on syphilis screening were updated in 2009 [guidelines of the International Union against Sexually Transmitted Infections (IUSTI)]. In low-risk populations, screening should start with a treponemal test (CLIA).[8,9] This is the best screening method for asymptomatic populations with high number of patients, as it is a fast automatic test, highly sensitive (95% - 99%) and specific (98% - 99%).[9-11] If positive, one confirmatory treponemal (TPHA) and one monitoring (therapeutic efficacy evaluation) non-treponemal test (VDRL or RPR) should be carried out.

An 8.9% percentage of patients with discrepant

Table 2 – Early syphilis: clinical classification

Early syphilis (n = 124)	No. of patients (%)
Primary	13 (10.5)
Secondary	71 (57.3)
Early latent	40 (32.2)

Table 3 – Results of treponemal tests (CLIA and TPHA)

		TPHA	
		Positive	**Negative**
CLIA	Positive	387	7
	Negative	0	Excluded

treponemal tests were found, from which seven were included and 45 were excluded due to false positive results. Exclusion from the study was due to the absence of a clinical history of syphilis and, in low-risk populations, due to being considered as false positive when CLIA is positive and the remaining treponemal and non-treponemal tests were negative.[9] However, Ooi *et al.*[12] found that a more comprehensive medical history would provide additional clinical data that would raise the clinical suspicion of syphilis in 32% of the patients.[12] Seven patients were included in our study despite the presence of inconsistent treponemal tests, including two patients with early syphilis and five with previously treated or late syphilis. Discrepant tests are more common in HIV carriers, which is in line with the results found in our study.

All serological tests for the diagnosis of syphilis have some limitations.[10] Detailed medical history with comprehensive epidemiological data and additionally repeated tests are very helpful for the interpretation of the results, showing the importance of clinical/laboratory correlation.[10]

Even though the identification of early syphilis is the priority in screening programs, the most recently diagnosed patients in the UK had a late infection.[11] An 11% percentage was found in our study and therefore the importance of a systematic screening of every admitted patient should be emphasized, in order to identify this stage of the disease. Since 16 June 2014, according to the Order no. 609-A/2014, late syphilis became also notifiable in Portugal, which will show in the future the full dimension of the problem.

CONCLUSION

The lack of resources for the promotion of sexual health education, the low levels of health awareness, as well as the presence of other STDs raise the risk of transmission of syphilis. In the 21st century, syphilis still is a public health issue and having a need for education, screening and follow-up programs aimed to reduce prevalence and improve partner notification and screening.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

FINANCIAL SUPPORT

The authors declare that there was no financial support in writing this manuscript.

REFERENCES

1. Tong ML, Lin LR, Liu GL, Zhang HL, Zeng YL, Zheng WH, et al. Factors associated with serological cure and the serofast state of HIV-negative patients with primary, secondary, latent, and tertiary syphilis. PLoS One. 2013;8:e70102.
2. ECDC (2013) - Surveillance Report: Annual epidemiological report – Reporting on 2011 surveillance data and 2012 epidemic intelligence data. [consultado 2015 jan 12]. Disponível em: http://www.ecdc.europa.eu/en/publications/Publications/Annual-Epidemiological-Report-2013.pdf.
3. Direção-Geral da Saúde. Doenças de declaração obrigatória 2009-2012 – Volume I. [consultado 2015 jan 12]. Disponível em: http://www.google.pt/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0CCMQFjAB&url=http%3A%2F%2Fwww.dgs.pt%2Fportal-da-estatistica-da-saude%2Fpublicacoes-estatisticas-146417-pdf.aspx%3Fv%3D11736b14-73e6-4b34-a8e8-d22502108547&ei=hM7HVJ2qMpaZsQT2ooCoCQ&usg=AFQjCNErfKOuiE2ON9cHI-JcUr8BolBgZw&bvm=bv.84349003,d.cWc.
4. Council of State and Territorial Epidemiologists. Recent changes to gonorrhea and syphilis case definitions: program impact. [consultado 2015 jan 12]. Disponível em: http://www.cdc.gov/std/stats/casedef-programimpact-2014.pdf.
5. Repiso B, Frieyro M, Rivas-Ruiz F, De Troya M. Condom use and number of sexual partners among male syphilis patients who report having sex with men. Actas Dermosifiliogr. 2010;101:847-52.
6. Zetola NM, Engelman J, Jensen TP, Klausner JD. Syphilis in the United States: an update for clinicians with an emphasis on HIV coinfection. Mayo Clin Proc. 2007;82:1091-102.
7. Ferreira O, Lisboa C, Ramos FM, Azevedo F. Sífilis numa consulta de infecções sexualmente transmissíveis – análise de 880 doentes. Rev Soc Port Dermatol Venereol. 2012;70:99-104.
8. Janier M, Hegyi V, Dupin N, Unemo M, Tiplica GS, Potocnik M, et al. European Guideline on the management of syphilis. Eur Acad Dermatol Venereol. 2015;29:1248.
9. Young H, Moyes A, Seagar L, McMillan A. Novel recombinant-antigen enzyme immunoassay for serological diagnosis of syphilis. J Clin Microbiol. 1998;36:913–7.
10. Park IU, Chow JM, Bolan G, Stanley M, Shieh J, Schapiro JM. Screening for syphilis with the treponemal immunoassay: analysis of discordant serology results and implications for clinical management. Infect J Dis. 2011;204:1297-304.
11. Young H. Guidelines for serological testing for syphilis. Sex Transm Infect. 2000;76:403-5.
12. Ooi C, Robertson P, Donovan B. Investigation of isolated positive syphilis enzyme immunoassay (ICE Murex) results. Int J STD AIDS. 2002;13:761-4.