Journal section: Oral Medicine and Pathology
Publication Types: Review

The reappearance of a forgotten disease in the oral cavity: Syphilis

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Viñals-Iglesias H, Chimenos-Küstner E. The reappearance of a forgotten disease in the oral cavity: Syphilis. Med Oral Patol Oral Cir Bucal. 2009 Sep 1;14 (9):e416-20.
http://www.medicinaoral.com/medoralfree01/v14i9/medoralv14i9p416.pdf

Received: 30/09/2008
Accepted: 20/03/2009

Article Number: 2466 http://www.medicinaoral.com/

eMail: medicina@medicinaoral.com
Indexed in:
-SCI EXPANDED
-JOURNAL CITATION REPORTS
-Index Medicus / MEDLINE / PubMed
-EMBASE, Excerpta Medica
-SCOPUS
-Indice Médico Español

Abstract
Syphilis is a sexually transmitted disease (STD) produced by Treponema pallidum, which mainly affects humans and is able to invade practically any organ in the body. Its infection facilitates the transmission of other STDs. Since the end of the last decade, successive outbreaks of syphilis have been reported in most western European countries. Like other STDs, syphilis is a notifiable disease in the European Union. In Spain, epidemiological information is obtained nationwide via the country's system for recording notifiable diseases (Spanish acronym EDO) and the national microbiological information system (Spanish acronym SIM), which compiles information from a network of 46 sentinel laboratories in twelve Spanish regions. The STDs that are epidemiologically controlled are gonococcal infection, syphilis, and congenital syphilis. The incidence of each of these diseases is recorded weekly. The information compiled indicates an increase in the cases of syphilis and gonococcal infection in Spain in recent years. According to the EDO, in 1999, the number of cases of syphilis per 100,000 inhabitants was recorded to be 1.69, which has risen to 4.38 in 2007. In this article, we review the reappearance and the evolution of this infectious disease in eight European countries, and alert dentists to the importance of a) diagnosing sexually-transmitted diseases and b) notifying the centres that control them.

Key words: *Syphilis, syphilis in Spain, syphilis in Europe, clinical manifestations, diagnosis.*

Introduction
Syphilis is a sexually-transmitted disease (STD) produced by *Treponema pallidum*, a microaerophilic spirochete which mainly infects humans and which is able to invade practically any organ in the body. Its infection facilitates the transmission of other STDs (1).

The presumptive diagnosis of the infection can be made clinically. However, a number of points should be borne in mind. First, dentists working today are less familiar with syphilis than their predecessors, who worked at times when the prevalence of the disease was higher; so they should be alert to suggestive oral lesions and include them in the list of differential diagnoses. Second, the oral and systemic clinical manifestations of syphilis may resemble those of other entities, and third, both the clinical manifestations and the habitual diagnosis may be masked by the presence of coinfection with other pathogens such as the HIV virus.

Syphilis has two main clinical stages: early and late. Early or infectious syphilis (recently acquired, or of less than two years' duration) is the more contagious stage, and includes the primary and secondary forms

and the early latent period. Primary syphilis appears after an incubation period of between one and four weeks, typically in the form of an erosive, indurated, painless chancre–usually only one–and always accompanied by regional, multiple, enlarged, rubbery and discrete adenopathies (2). Nonetheless, primary syphilis is often asymptomatic; the initial lesion is genital in approximately 85% of cases, anal in 10%, and oropharyngeal in 4% (3). After 4-6 weeks the infection spreads through the blood and the lymph vessels, presenting non-specific signs and symptoms and disseminated mucocutaneous and systemic lesions. The clinical manifestations of the secondary form are polymorphous, and syphilids are the most frequently found mucocutaneous lesions. Mucosal plaques (Fig.1 and 2) are the most frequent oral manifestation of this secondary stage; the organs are not usually affected. Tertiary syphilis, which is extremely rare, may appear three years or more after the initial infection. The characteristic lesion is the gumma, which in the oral cavity may affect the palate, the tongue or the tonsils (2).

Fig. 1. Mucosal plaque of secondary syphilis in the retrocommissural area.

Fig. 2. Syphilid on the edge of the tongue in a male homosexual.

The decisive breakthrough in syphilis treatment was made in the 1940s, with the introduction of penicillin and the success of the prevention campaigns carried out in the US and Europe. After this spectacular reduction, the disease re-emerged in the 1960s due to a series of behaviours that we will call the "three p's" –permissiveness, promiscuity, and the pill. In the 1970s, with the application of new control measures, the prevalence fell once more. Since then, in industrialized countries, the pattern of behaviour of syphilis consists of sudden rises in the numbers of individuals infected, followed by periods of low prevalence every 5 to 10 years. In 1999, unprecedentedly low rates of syphilis were recorded in the US (2.5 cases/100,000 inhabitants), due to the influence of HIV prevention campaigns (4). Today, however, after the effective control of AIDS in the US and Europe, preventive measures in sexual behaviour are becoming relaxed, and this relaxation has contributed to the appearance of new outbreaks of syphilis (and of other STDs) – especially among male homosexuals, in whom the proportion of HIV positives is higher than average (5-14), Without greater control of the situation, new outbreaks of syphilis (and AIDS and other STDs) are to be expected in industrialized countries. Adequate preventive measures are required not only in the practice of ano-genital sex but in oral sex as well (7,9,10, 15-17). In the latter case, the oral cavity is the gateway to infection.

The situation in Spain

Like other STDs, syphilis is a notifiable disease in European Union countries. In Spain, nationwide epidemiological information is obtained from the EDO and the SIM, which compile information via a network of 46 sentinel laboratories in twelve of the country's regions. The STDs that are epidemiologically controlled are gonococcal infection, syphilis and congenital syphilis, the number of cases of these diseases being recorded weekly. The information compiled indicates in recent years an increase in the cases of syphilis and gonococcal infection notified in Spain. In fact, the EDO records show that the rates of syphilis rose from 1.69 per 100,000 inhabitants in 1999 to 4.38 per 100,000 inhabitants in 2007 (18,19). However, since numerical recordings do not provide data on the characteristics of the new cases notified, in May 2005 an STD working group was set up, comprising 14 diagnosis centres from seven regions of Spain. In Catalonia, the rate of syphilis was 3.7 cases/100,000 inhabitants in 2005 (an increase of 176.1% over 2000) and 5.2 cases/100,000 inhabitants in 2006 (12).

The situation in the European Union

In the European Union, the reference centres for epidemiological surveillance of STDs provide relatively

thorough and accurate information on the current state of syphilis. Constant efforts are made to improve the notification systems (6-10).

As a response to the outbreak in Europe, the ESSTI (The European Surveillance of Sexually Transmitted Infections) set up a working group to study preventive measures in use against HIV/syphilis in MSM (men who have sex with men) (9).

(Table 1) shows the cases of infectious syphilis in the EU. We compared epidemiological data in several ur-

Table 1. The cases of infectious syphilis in the EU.

COUNTRY-REGION-CITY	YEAR	CHARACTERISTICS
SPAIN (15-16,24) (Barcelona)	2002-2003	95% males Mean age 34 years 86% MSM* *(Men who have Sex with Men)* 68% born in Spain 19% born in Latin America 9% from Eastern European countries 37% VIH+ high incidence of Hepatitis A
BELGIUM (6) (Antwerp, Brussels)	Oct 2000- Mar 2004	93.4% males Mean age (males) 37 years 79,9% MSM 14,7% heterosexuals 76,1% born in Belgium 9,8% other European nationalities 4,3% born in Latin America 50,5 % VIH+ 25,9% history of Hepatitis B
DENMARK (11) (Copenhaguen)	2003-2004	96% males 78% MSM 75% resident in the Copenhagen area 70% syphilis acquired "domestically" 37% of MSM were HIV +
FRANCE (7) (Île de France, Paris)	2000-2003	Mean age (males) 36,5 years 75-87% MSM 70 % born in France 83% relations with "casual" sexual partners 33-60 % VIH+.
GERMANY (8) (Frankfurt, Cologne, Berlin, Hamburg, Munich)	1997-2003	75% MSM High nº of heterosexuals cases prevalence > 50% of VIH + among MSM
REPUBLIC OF IRELAND (9) (Dublin)	Jan 2000- Dec 2003	88,1% males Mean age (males) 35 years 66,5% homosexuals 83,6 % MSM 31% of MSM practised unprotected oral sex 68,9% patients born in Ireland 18,1% patients born outside Ireland High prevalence among VIH+
CZECH REPUBLIC (21)	1994-2001	incidence: 3,6-9,6/100.000 inhab. higher prevalence in urban areas with high levels of prostitution high prevalence among refugees high incidence of congenital syphilis (0.1-0.2/ 100.000 inhab.)
UNITED KINGDOM KINGDOM (10) (London)	April 2001-Set 2004	66% MSM 32,3% heterosexuals 89% white homosexuals born in the United Kingdom high incidence among blacks not born in UK high rates of prostitution 53% of MSM were HIV +

ban areas with high rates of incidence in eight European countries: Spain (Barcelona), Denmark (Copenhagen), Belgium (Antwerp and Brussels), France (Île de France and Paris), Germany (Frankfurt, Cologne, Berlin and Hamburg), Republic of Ireland (Dublin), the Czech Republic and the United Kingdom (London).

Cases of syphilis were defined in accordance with the recommendations of the WHO and the European authorities (20). These include the clinical presumptive diagnosis and direct visualization of spirochetes in clinical samples (or more often in serology tests, since *Treponema pallidum* cannot be cultivated *in vitro)* (6-8,21).

Diagnostic Tools

In addition to clinical suspicion and direct visualization of spirochetes, two types of serology test are available (1,22):

a) non-treponemic tests–VDRL or RPR–which are based on the detection of antibodies Ig M or Ig G (reagins) in the serum of patients with syphilis which react to antigens containing cardiolipin-cholesterol-lecithin; these tests are inexpensive and are used for screening or follow-up of treated patients.

b) treponemic tests based on absorption (FTA-ABS), microhemagglutination (MHA-TP) and agglutination (TPPA), are used for confirmatory purposes if the non-treponemic tests are positive. Epidemiological data are also obtained from patients with syphilis, and tests for HIV are performed.

Therapy

The treatment of choice for primary and non-complicated secondary syphilis is a single dose of penicillin G benzathine of 2.4 million UI administered by intramuscular route. In the case of allergy, doxycycline may be used (100mg administered orally, twice a day for two weeks) or tetracycline, which offers similar levels of efficacy (23). In general, HIV patients can be treated in the same way as seronegative patients (1).

Discussion

We found certain similarities in the syphilis outbreaks in the different European countries studied. The prevalence of the disease among male homosexuals is higher than among heterosexuals in almost all the areas under analysis. The highest number of cases recorded corresponds to men who have sex with other men (MSM), who in many cases were aware of their coinfection with HIV; these findings suggest that male homosexuals remain a reservoir for syphilis, presenting an increase in high-risk sexual behaviours and a reduction in the use of protective measures. For example, in Barcelona, 4% of cases of primary syphilis are located in the oropharynx (3), supporting the notion that some syphilis outbreaks are due to the practice of unprotected oral sex. The prevalence of syphilis in women is lower than in men in Europe. Though most infected patients were living in their native country, some cases were immigrants or refugees (in Spain, Belgium, Ireland, Germany, the Czech Republic and the UK). The infection is more frequent in the large cities or in the surrounding regions. (6-10,15,16,24).

There are many reasons for the increase in prevalence of the disease. The main cause is the practice of unprotected ano-genital and oral sex. The lifestyle of many subjects is characterized by risk situations, such as frequenting saunas, bars, and clubs in search of casual contacts (9), blind dates arranged in Internet; low-cost travel between different European countries and the activity of prostitution networks imported from south-eastern and eastern Europe have also increased prevalence (5).

An aspect that is difficult to assess is the influence of HIV on syphilis. Atypical forms of syphilis have frequently been reported in HIV-positive patients, with a faster course and with more florid systemic manifestations than in the seronegative population (1,25). Primary syphilis is often asymptomatic and the initial lesion is extragenital in a considerable number of cases (26,27). Secondary syphilis and latent infection are the most usual forms of presentation in HIV positive patients (25,28). Skin lesions in the form of generalized maculopapular eruptions are the most common manifestations of secondary syphilis (1,28). The presence of HIV in the diagnosis of syphilis may alter the serological response. First, HIV-positive patients may present negative serology during the primary and secondary syphilis more often than in the general population; second, the rates of false negatives in the reagin tests due to the prozone effect (antigen excess) is greater; third, the reagin tests may remain positive in a greater number of cases and for a longer period of time (1). If conventional serology does not confirm syphilis in the case of clear clinical suspicion, PCR techniques using DNA polymerase I sequences have demonstrated sensitivity and specificity between 80-98% in the case of early syphilis (29). Patients coinfected with HIV and syphilis present a higher prevalence of treatment failure; nonetheless, as we mentioned above, treatment is the same as for non-HIV patients (1).

If we examine the other direction–that is, the influence of syphilis on HIV–it appears clear that the ulcerous lesions are related to an increased risk of HIV infection, since the chancre may be the infection's access route. In addition, it has been reported that syphilis may increase immunological activation and cytokine secretion, thus favouring the replication of the virus (1). Recent studies have shown an increase in the viral load and a fall in the lymphocyte CD4 count in patients with HIV and

early syphilis (30), which obviously has a bearing on the control of the HIV infection.

The comparison by countries (Table 1) shows that the rate of coinfection of syphilis and HIV varies according to the population analysed, together with other individual risk factors. However, given the ease of contact between different countries, these rates will tend to even out. To minimize the risk of spread of the infection, dentists have an important part to play in prevention and rapid diagnosis.

Conclusion

Dentists must be aware of the oral and systemic manifestations of the primary and secondary forms of syphilis, and should refer the cases they diagnose to the reference centres for sexually-transmitted diseases. The possible association of syphilis with HIV and with other STDs should not be forgotten. Finally, dentists must inform their patients of the need to take preventive measures, not only in the practice of genital-anal sex but also in oral sex, which is often overlooked.

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Acknowledgements:
We thank Dra. Mª Mercè Alsina for her collaboration.