SYPHILIS AMONG STD CLINIC PATIENTS IN PRAGUE IN 2009

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SUMMARY

The aim of the study was to evaluate clinical, epidemiological and demographic data of patients with syphilis hospitalized at the Department of Dermatovenereology of the General Teaching Hospital in 2009 and to identify the groups at high risk of sexually transmitted diseases. The results were compared with the previous surveys carried out between 1999 and 2005 and also with the data of the National Registry of Venereal Diseases for 2008.

A total of 232 patients were hospitalized in 2009 (including 26 women admitted for compulsory retreatment in pregnancy). We noticed a 25% increase in the number of patients in comparison with the year 2008. Of the total number of patients, 206 were patients with newly diagnosed syphilis, of which 153 (74.3%) were men and 53 (25.7%) women. There was 22.3% of patients with primary and 31.6% with secondary syphilis. As in the previous years, heterosexual contact remained the most frequent route of syphilis transmission. However, the number of homosexual and bisexual men increased, amounting to 64.7% of all hospitalized men. Four men were HIV positive. The age distribution did not change; majority of the patients were aged between 30 and 40. The proportion of foreigners also remained unchanged (19.9%); they came mainly from the Slovak Republic (31.1%) and Ukraine (26.7%). The absolute number of reported syphilis cases has been increasing in the Czech Republic since 2006. From the epidemiologic point of view, the increasing incidence of early stages of the disease is alarming. Men prevail over women among the infected persons; the men having sex with men (MSM) has been increasing in the last three years.

Key words: syphilis, Prague, epidemiology, symptoms, risks

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INTRODUCTION

Sexually transmitted diseases (STDs) other than HIV are important global health issues. They have, however, been neglected as a public health priority and control efforts continue to fail (1). Syphilis, like many other STDs, facilitates the spread of HIV by increasing the likelihood of transmission of the virus. Syphilis may increase HIV replication and immune demage. Conversely, HIV may speed treponemal dissemination and disease severity (2, 3).

Syphilis, a genital ulcerative disease, is highly infectious, but easily curable in its early (primary and secondary) stages. If untreated, it can lead to serious longterm complications, including brain, cardiovascular, and organ damage, and even death. Syphilis is classified as acquired or congenital. Congenital syphilis can cause stillbirth, death soon after birth, and physical deformity and neurological complications in children who survive. Acquired syphilis is divided into early- and late-syphilis. Early (infectious) syphilis: primary, secondary and early latent infection. The European Centre for Disease Prevention and Control (ECDC) defines early syphilis as syphilis acquired <1 year previously and the World Health Organization (WHO) defines early syphilis as syphilis acquired <2 years previously (4, 5). Late syphilis: late latent and tertiary syphilis (gummatous, cardiovascular and neurosyphilis).

Clinical Manifestations

Clinical manifestations separate the disease into stages. Infection is initiated when *T. pallidum* penetrates dermal microabrasions or intact mucous membranes, typically resulting in a single chancre at the site of inoculation. Moderate regional lymphadenopathy is associated with the primary stage. The chancre usually becomes indurated and will progress to ulceration but typically is not purulent. Within hours of inoculation, and during the evolution of the primary stage, *T. pallidum* disseminates widely and organisms are deposited in a variety of tissues (2).

Sore throat, muscle aches, malaise, and weight loss are examples of variable systemic symptoms of secondary syphilis. Generalized nontender lymphadenopathy occurs in up to 85% of cases. The most common manifestation of secondary syphilis is a disseminated mucocutaneous rash. Pale and discrete macular lesions appear initially on the trunk and proximal extremities; these are followed by lesions of various morphologies among patients. At diagnosis, the most common types of secondary syphilis lesions are maculopapular (in 50% to 70% of patients), papular (12%), macular (10%), and annular papular (6% to 14%) (6, 7, 8). Rash is frequently found on the palms of the hands and soles of the feet and, in 4% to 11% of patients, *T. pallidum* infection of hair follicles results in alopecia of the scalp. There have also been infrequent reports of facial and body hair loss. Concurrent with the appearance of secondary lesions, about 10%

of patients develop condylomata lata. These enlarged lesions, appearing in warm and moist areas including the perineum and anus, are highly infectious. Localized inflammation of the oral cavity, tongue, and genital mucous membranes can cause mucous patches (9, 10); infrequently, secondary syphilis can be accompanied by gastric and renal involvement and hepatitis (11). Approximately 5% of individuals with secondary syphilis experience the early manifestations of neurosyphilis, including meningitis and ocular disease (6). Latency is the period between healing of the clinical lesions and appearance of late manifestations, and it can last for many years. About 70% of untreated individuals will remain in this stage for the rest of their lives. Latency is characterized by positive serologic tests for specific antibodies without clinical signs or symptoms. Infectivity may occur intermittently due to the presence of treponemes in the bloodstream, and pregnant women with latent syphilis may infect the fetus in utero. The tertiary stage is also called late syphilis and is characterized by the presence of a small number of organisms and a high cellular immune reactivity against the organism. Signs of late syphilis can be recognized in approximately one-third of untreated individuals several months to years after being infected with treponemes. The microorganisms can invade the central nervous or cardiovascular systems and the skin (as well as other organs) and lead to damage due to host delayed-type hypersensitivity responses, which produce local inflammation and gummas in affected tissues.

Vaccine Development

Up until now, there is no usable vaccine available. There are several reasons why active syphilis vaccine development efforts should continue. These include prevention of HIV transmission, prevention of congenital syphilis in developing nations and, last but not least, prevention of the possible serious late sequelae of untreated syphilis.

In many studies, immunization with *T. pallidum* molecules (e.g. endoflagella, Gpd, TmpB, Tp92, TpN15, TpN47, TprF) was conducted and protection against infectious challenge was determined. Immunization stimulated the production of strongly reactive antibodies, some of which were shown to be opsonic. These immunization regimens, however, induced only partial protection, shown by attenuated development and rapid healing of lesions. This lack of complete protection in the face of high antibody titers suggests that the cellular immune response is critical to early clearance of *T. pallidum*. The requirement for cellular immunity in syphilis protection is supported by the fact that passive transfer of antibodies against *T. pallidum*, or against one of its lipid components, does not completely protect against infection. Additionally, the recombinant molecules used for immunization in many of these studies are likely not to be folded in native conformation; thus, antibodies that bind to conformational epitopes of native antigen may not be produced by immunization. Finally, the first targets of the immune response, outer membrane proteins, are very rare in *T. pallidum*. The identification of molecules found on *T. pallidum's* surface is likely to be essential for the development of an effective syphilis vaccine. It is hoped that their discovery and use in a multivalent vaccine will lead to the production of an effective vaccine for syphilis (2).

Epidemiology

Syphilis is distributed worldwide and is particularly problematic in developing countries, where it is a leading cause of genital ulcer disease. The World Health Organization estimates that 12 million new cases of syphilis occur each year (12). Numbers and rates of infectious syphilis fell to their lowest levels in many European Union (EU) countries by the early 1990s (13, 14), despite substantial increases in syphilis incidence in Russia (15, 16). The decreases in western Europe were accompanied by marked reductions in the incidence of congenital syphilis and tertiary disease. By 1995, with the exception of Germany, fewer than 300 cases of infectious syphilis were recorded in any of the reporting EU countries. Since 1996, syphilis has again been on the increase in many northern and western EU countries (17), in part driven by increases in cases among men who have sex with men, although more recent increases among heterosexual people have also been reported. An increase in new cases has also been noted in eastern Europe since the dissolution of the Soviet Union. The number of reported cases increased dramatically in the Russian Federation, from 7,911 in 1990 to 392,616 in 1997, with a similar phenomenon observed in other Eastern European countries (18).

In the Czech Republic most cases of syphilis, total of 18,000 were diagnosed after the World War II during the mass screening of the population aged 15 to 40 years in 1951 (the "PN – venereal diseases action"). In the following years, the incidence of syphilis decreased considerably, the yearly incidence being in the range of hundreds. The incidence of syphilis has increased rapidly and substantially during the 1990s as a result of geopolitical and socioeconomic changes. The syphilis rate has risen eightfold, from 1.6 per 100,000 inhabitants in 1990 to 13.5 per 100,000 inhabitants in 2001 due to high proportion of syphilis cases among immigrants (Fig. 1). The proportion of immigrants rose from 5.4% in 1990 to 59% in 2001. Foreign patients came mainly from the Ukraine (42%), Moldavia (12.5%), the Russian Federation (8%), and Georgia (8%). From the epidemiologic point of view, the growth of the proportion of early syphilis (diagnosed within 2 years of infection) was significant in the 1990s. In 1990, the early form represented 24.4% of the total number of notified cases; in 1998 it had climbed to 65.6%. Since 2000, there has been an increase in the number of cases designated as late latent or of unknown duration, which represent 68.6% of the total number of reported cases in

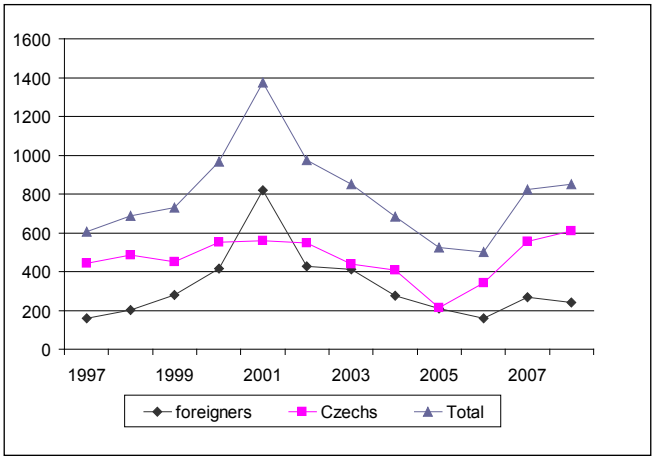

Fig 1. *Number of syphilis cases in the Czech Republic.*

2005. Groups at increased risk for syphilis remain cohorts of men aged 25 to 29 years, and 30 to 34 years, with a peak at 30 years of age. The age distribution of women patients is wider, beginning in the 15- to 19-year age group and peaking at 25 years of age. The increase of infectious syphilis was also reflected in the occurrence of congenital syphilis. In 1998, 66 cases of syphilis in pregnant women and 18 cases of congenital syphilis were reported, the highest numbers since 1960 (19, 20, 21). After reaching a peak in 2001, the incidence of syphilis has been decreasing. After 2006, the incidence has increased again and the majority of these cases are in males. Migration of foreigners from Eastern Europe is likely to continue influencing the syphilis rates in the Czech Republic (20).

METHODS

A surveillance of new onset syphilis cases was conducted from the 1st January 2009 to the 31st December 2009 at the Department of Dermatovenereology of the General Teaching Hospital in Prague, which is the reference center for approximately 50% of the Prague population. Syphilis cases were diagnosed based on clinical features, the serologic picture, and dark-field microscopy and based on analysis of the hospitalization records

RESULTS

Of the total number of 232 patients hospitalized with syphilis in 2009 (including 26 women admitted for compulsory retreatment in pregnancy), 206 were patients with newly diagnosed infection, of which 153 (74.3%) were men and 53 (25.7%) women. The data are shown in Tables 1–3. The male-female ratio was 3:1. As in 2008, the majority of men were aged 30 to 40 (34.6%) and over 40 (29.4%). Most of women belonged to the age group of 25–29 and 30–40 (43.4%). There were 41 (19.9%) foreigners among the hospitalized patients, of which 26 (63.4%) were men and 15 (36.6%) women. As for the marital status, most of the patients were single, amounting to a total of 150 (72.8%) persons, out of whom 117 were men (76.5%) and 33 women (62.3%). Approximately the same number of men and women were divorced (11.1% and 11.3%). Most women had only basic education (69.8%). From the total number of patients, 47 (22.8%) were unemployed.

Among men, there were 99 (64.7%) men having sex with men (MSM). The majority of men had more than one sexual partner at the time of supposed syphilis infection (57.3%). Equal number of men and women evaluated their sexual behaviour as promiscuous (16.5%). Prostitution was reported by 4 men (2.6%) and 13 (24.5%) women. Compared to the previous surveys, significantly more men (7.8%) and especially women (20.8%) were injecting drug users. There were 116 (56.3%) cigarette smokers. A total of 46 patients (22.3%) were identified by contact tracing, 9.7% of patients were sent by their dermatologist; all of them were men. A total of 38.3% of patients came due to clinical symptoms without recommendation from any health facility. Only 2.9% of patients were admitted based on the result of a preoperative examination, 15.0% patients came on the basis of a preventive check-up. Four patients (1.9%) were admitted with a serological relapse diagnosed within the follow-up treatment; all of them

Table 1. *Demographic data*

Sex		Men		Women		Total	
		No.	%	No.	%	No.	%
		153	**74.3**	**53**	**25.7**	**206**	**100.0**
Nationality	Czech	127	83.0	38	71.7	165	80.1
	Foreigners	26	17.0	15	28.3	41	19.9
Country of birth	Slovak	11	42.3	3	20.0	14	34.1
	Ukraine	3	11.5	9	47.4	12	29.3
Permanent address	Prague	88	57.5	23	43.4	111	53.9
	Other	65	42.5	30	56.6	95	46.1
Age	15–19	0	0.0	3	5.7	3	2.0
	20–24	18	11.8	8	15.1	26	12.6
	25–29	37	24.2	12	22.6	49	23.8
	30–40	53	34.6	23	43.4	76	36.9
	>41	45	29.4	7	13.2	52	25.2
Marital status	Married	18	11.8	14	26.4	32	15.5
	Single	117	76.5	33	62.3	150	72.8
	Divorced	17	11.1	6	11.3	23	11.2
	Widow	1	0.6	0	0.0	1	0.5
Education	<High school	65	42.5	37	69.8	102	49.5
	High school	49	32.0	14	26.4	63	30.6
	University	39	25.5	2	3.8	41	19.9

Table 2. *Behaviour characteristics*

		Men		Women		Total	
		No.	%	No.	%	No.	%
Sexual orientation	MSM	99	64.7	0	0.0	99	48.5
	Heterosexual	54	35.3	53	100.0	106	51.5
Prostitution		4	2.6	13	24.5	17	8.3
Number of sex partners. past 12 months	1	30	19.6	25	47.1	55	26.7
	2–3	74	48.4	10	18.9	84	40.8
	Promiscuous	25	16.3	9	17.0	34	16.5
	No records	24	15.7	9	17.0	33	16.0
Cigarette smokers	Yes	89	58.2	27	50.9	116	56.3
	No	59	38.6	25	47.2	84	40.8
	ex-smoker	5	3.2	1	1.9	6	2.9
Injecting drug users		12	7.8	11	20.8	23	11.2

were men, 9.2% patients were admitted with re-infection. Of the 171 (83.0%) patients with early syphilis (diagnosed within 2 years of infection), 141 (92.2%) were men and 30 (56.6%) were women. Symptomatic syphilis was diagnosed in 111 cases (alone or in combinations), a total of 46 (22.3%) patients (43 men and three women) had a genital chancre. Extra-genital chancre was found in four cases, two men (lips) and two women (upper lip and tongue). Dark-field microscopy was positive in 20 (9.7%) cases. Most of the patients were treated with penicillin antibiotics; seven patients received doxycycline because of known allergy to penicillin. Jarisch-Herxheimer (JH) reaction (pronounced febrile reaction accompanied by an aggravation of the syphilitic symptoms) occurred in 83 (40.3%) patients, 72 men and 11 women. JH reaction was observed in nearly three quarters of patients with symptomatic syphilis. Of the total number of men, 5.9% had had gonorrhoea in the past. Gonorrhoea/syphilis co-infection was diagnosed in 9 men and 3 women. Hepatitis C, which is not routinely tested in syphilis patients, was newly diagnosed in 2 men and 1 woman. Mycoplasma infections were identified in 1 man and 5 women. Four men were HIV positive; three of them were MSM; all were single; one of them was newly diagnosed and admitted promiscuous behaviour.

DISCUSSION

All clinicians and laboratories in the Czech Republic have a statutory obligation to complete case reports of syphilis, gonorrhoea, ulcus molle, lymphogranuloma venereum, or granuloma inguinale and send them to the Department of Epidemiology of

Table 3. *Clinical data*

		Men		Women		Total	
		No.	%	No.	%	No.	%
Referred by	Contact tracing	29	19.0	17	32.1	46	22.3
	General practitioner	5	3.3	1	1.9	6	2.9
	Dermatologist	20	13.1	0	0.0	20	9.7
	Gynaecologist	0	0.0	3	5.7	3	1.5
	Self-referred. asymptomatic	4	2.6	1	1.9	5	2.4
	Self-referred. symptomatic	75	49.0	4	7.5	79	38.3
	Preventive screening	18	11.8	13	24.5	31	15.1
	Preoperative examination	2	1.3	4	7.5	6	2.9
	Antenatal clinic	0	0.0	10	18.9	10	4.9
Symptoms *	Discharge	10	5.3	1	1.6	11	4.4
	Ulcers	52	27.5	5	8.1	57	22.7
	Exanthema	37	19.6	3	4.8	40	15.9
	Fear from STD	31	16.4	10	16.1	41	16.3
	Partner's infection	29	15.3	17	27.4	46	18.3
	Prevention	11	5.8	12	19.4	13	5.2
	Treatment	19	10.1	14	22.6	33	13.2

Dark-field microscopy	Missing	115	75.2	48	90.1	163	79.1
	Positive	16	10.4	4	7.5	20	9.7
	Negative	22	14.4	1	1.9	23	11.2
Character of infection	First time	131	85.6	52	98.1	183	88.9
	Serological relapse	4	2.6	0	0.0	4	1.9
	Re-infection	18	11.8	1	1.9	19	9.2
Symptomatic syphilis *	Missing	57	37.3	38	71.7	95	46.1
	Present	96	62.7	15	28.3	111	53.9
	Chancre	47	30.7	3	5.7	50	24.3
	Macular or papular rash	50	32.7	7	13.2	57	27.7
	Condylomata lata	5	3.3	5	9.4	10	4.8
	Lymphadenitis	35	22.9	4	7.5	39	18.9
	Angina syphilitica	5	3.3	3	5.7	8	3.9
	Palmoplantar syphilis	11	7.2	1	1.9	12	5.8
	Alopecia	1	0.6	0	0.0	1	0.5
Stage of syphilis	Primary	43	28.1	3	5.7	46	22.3
	Early secondary	55	35.9	10	18.9	65	31.6
	Early latent	43	28.1	17	32.0	60	29.1
	Late latent	12	7.8	23	43.4	35	17.0
Treatment	Procaine PNC G + Benzathine PNC**	91	59.5	27	50.9	118	57.3
	Benzathine PNC	55	35.9	25	47.2	80	38.8
	Aqueous cryst. PNC + Benzathine PNC***	1	0.7	0	0.0	1	0.5
	Doxycycline	6	3.9	1	1.9	7	3.4
Jarish-Herxheimer reaction	Yes	72	47.1	11	20.8	83	40.3
	No	81	52.9	42	79.2	123	59.7
HIV tested at our department	Yes	97	63.4	19	35.8	116	56.3
	No	56	36.6	34	64.2	90	43.7
co-infections	Gonorrhoea	9	5.9	3	5.7	12	5.8
	Chlamydial infection	7	4.6	1	1.9	8	3.9
	Mycoplasma infections	1	0.7	5	9.4	6	2.9
	HIV	4	2.6	0	0.0	4	1.9
History of STD infection		37	24.2	10	18.9	47	22.8

* multi-response answer
** Procaine penicillin G. plus Benzathine penicillin G
*** Aqueous crystalline penicillin plus Benzathine penicillin

the Public Health Offices. Accredited epidemiologists cooperate with clinicians and laboratories in checking reported data, confirmation of diagnosis, treatment, and examination of contact persons. This information is then transferred to the National Registry of Venereal Diseases (NRVD). Statistically processed anonymous data are classified by individual diagnosis, age, sex, patient's residence, and other factors, and the outputs are made available regionally on a quarterly basis and annually for the entire country. Annual reports are edited by the Czech Ministry of Health's Institute of Health Information and Statistics. Relevant issues cover the data on syphilis, gonorrhoea, chancroid, and lymphogranuloma venereum going back to 1959 (21, 22). Czech legislation stipulates that syphilis patients must be treated in the hospital only. A retrospective case note review of patients diagnosed and hospitalized with acquired syphilis in 2009 at the Department of Dermatovenereology was performed.

Our data on Prague's population basically correspond with the nationwide records. The reason for the rising syphilis notification rate has been credited to the political and socioeconomic changes in the Czech Republic in 1989 that have resulted in increased travel, economic migration, income differentials, dramatic increases in commercial sex and more open sex industry. From the epidemiologic point of view, the increase of the number of early infectious forms is significant. Their proportion was highest in 1996 (71.0%), declined to 35% in 2006 and rose again to 60.3% (4.9 cases per 100,000 inhabitants) in 2008. In our patients, the increased incidence of early forms is even more significant. Another trend is an increase in the number of infected men. While the proportion of hospitalized men and women was equal until 2006, in the last three years, we have recorded an increase among males, the male-female ratio being 3:1 in 2009. Compared to the previous study from 1999–2005, we have seen a significant

increase of syphilis incidence in MSM (19, 23). This trend corresponds to the situation in developed West European countries. In the developed European countries and USA, isolated outbreaks can be observed in homosexual communities, which are accounted for by the improved health condition of HIV-infected men, the highly active antiretroviral therapy and its better accessibility, the use of methamphetamine and Viagra and unprotected oral and anal intercourses (17, 24, 25). These minor outbreaks were described for example in Dublin in 2001 through 2003, where 31% of homosexual men reported an unprotected oral intercourse and 15.9% unprotected anal intercourse (26). Similar findings have been reported from Manchester, Bristol and London (27, 28). In Denmark in 2004, homosexual men accounted for 78% of all newly reported cases, 37% of them being HIV-positive (29). Similar data were reported from Belgium and Germany. In 2003, the syphilis incidence in Germany was 10 times higher among men than among women (75% of them being homosexuals and 50% HIV-positive). According to foreign studies, HIV/syphilis co-infection in homosexual men ranges from 20 to 73% (27, 30, 31). The data on HIV/syphilis co-infection rates are lower among our patients, which is in concordance with relatively low HIV prevalence in the Czech Republic. From the launch of the National HIV/AIDS Monitoring Program to December 31, 2009, as many as 1,344 HIV-positive patients were recorded in the Czech Republic, of whom 292 were diagnosed as having fully developed AIDS that resulted in 156 deaths. The Czech Republic notified 157 new HIV cases which was about 10 more then in 2008. Sexual contact remains the most frequent mode of HIV transmission in the Czech Republic, accounting for 91% of the total number of cases registered to date. MSM are at the highest risk of HIV transmission (64.3% of newly diagnosed HIV cases in 2009). The current reporting system does not capture data on HIV and syphilis co-infection; including these data into the reporting system would be important for initiating targeted prevention measures (32). In heterosexual men, primary chancres most commonly occur on the penis, but 32 to 36% of homosexual men have primary chancres in other sites, including the rectum, anal canal, and oral cavity (33, 34). The extragenital lesions among our patients were rare, suggesting that they were overlooked by the patients.

CONCLUSIONS

In the last four years, we have seen an increase in the number of syphilis cases among patients treated at the Department of Dermatovenereology in Prague, in line with nationwide trends. The age distribution did not change; majority of the patients were aged between 30 and 40. The proportion of foreigners also remained unchanged; they came mainly from the Slovak Republic and Ukraine. The increasing number of early symptomatic infections and infected homosexual men are the most significant epidemiologic findings, although heterosexual contact remained the most frequent route of syphilis transmission. This trend confirms the importance of contact-tracing, HIV and syphilis testing and the presumptive negative consequences of the abandonment of the serologic screening during the first hospitalization in the given year, which is no longer required by Czech legislation. Interventions delivered to whole populations, or groups in whom the risks of infection and onward transmission are very high, have the greatest potential effect. Effective action requires a multifaceted approach including better basic epidemiological and surveillance data supported by high quality evidence about effectiveness of individual interventions and programmes (1).

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