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ORIGINAL ARTICLE

Characterization of genital herpes population: a retrospective study in a tertiary center in Lisbon

Caracterização da população com herpes genital: estudo retrospetivo num centro terciário em Lisboa

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Abstract

Objective: Genital herpes (GH) is one of the most common sexual transmitted infections. Herpes simplex virus type 1 (HSV-1) genital infections have been increasing, with a shift toward its predominance in many developed countries. The aim of this study was to characterize the population with GH diagnosed in Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal. **Methods:** A retrospective analysis of all laboratory-confirmed diagnosis of GH between 2017 and 2021 was conducted. The diagnosis was established by real-time polymerase chain reaction, in samples collected by swabbing suspicious mucocutaneous lesions. Medical records of included patients were reviewed and data of interest analyzed. **Results:** During the studied period, a total of 239 patients were diagnosed with GH, from which 76.6% (n = 183) were caused by HSV type 2 (HSV-2). Most patients were men (68%; n = 163), with a mean age of 35.7 years. Compared to the group diagnosed with HSV-2, the mean age was significantly lower in the HSV-1 group (28.6 years vs. 37.9; $p < 0.001$) and the proportion of patients with first clinical manifestations of GH was significantly higher in the latest (67.8% vs. 30%; $p < 0.001$). Concomitant infection with human immunodeficiency virus was detected in 17.6% of the subjects, being significantly more prevalent among men and within the HSV-2 group ($p = 0.018$). **Conclusions:** HSV-2 remained the most common cause of GH throughout the study. Even so, similar to other European studies, HSV-1 patients were younger and the proportion of initial infection in this group was significantly higher.

Keywords: Genital herpes. Sexual transmitted infections. Epidemiology.

Resumo

Objetivo: O herpes genital (HG) é uma das infeções sexualmente transmissíveis (IST) mais comuns. As infeções genitais pelo vírus herpes simples tipo 1 (HSV-1) têm aumentado, com uma mudança no sentido da sua predominância em muitos países desenvolvidos. O objetivo deste estudo foi caracterizar a população com HG diagnosticada no Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal. **Métodos:** Foi realizada uma análise retrospetiva dos diagnósticos de HG confirmados laboratorialmente entre 2017 e 2021. O diagnóstico foi estabelecido por PCR em tempo real, em amostras colhidas por zaragatoa de lesões mucocutâneas suspeitas. Foram revistos os registos clínicos dos doentes incluídos e analisados os dados de interesse.

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Resultados: No período de estudo, 239 doentes foram diagnosticados com HG, dos quais 76.6% (n = 183) foram causados pelo HSV tipo 2 (HSV-2). A maioria dos doentes eram do sexo masculino (68%; n = 163), com idade média de 35.7 anos. Em comparação com o grupo diagnosticado com HSV-2, a idade média foi significativamente menor no grupo HSV-1 (28.6 anos vs. 37.9; p < 0.001) e a proporção de doentes com manifestação clínica inicial de HG foi significativamente maior neste último (67.8% vs. 30%; p < 0.001). A infeção concomitante pelo vírus da imunodeficiência humana foi detetada em 17.6% dos indivíduos, sendo significativamente mais prevalente entre homens e no grupo HSV-2 (p = 0.018). **Conclusões:** O HSV-2 foi a causa mais comum de HG durante todo o estudo. Ainda assim, à semelhança de outros estudos europeus, os doentes com HSV-1 eram mais jovens e a proporção de infeção inicial neste grupo foi significativamente maior.

Palavras-chave: Herpes genital. Infeções sexualmente transmissíveis. Epidemiologia.

Introduction

Herpes simplex virus (HSV) is one of the most ubiquitous human infections[1]. In 2016, the World Health Organization estimated that globally, 3.7 billion people under the age 50 had HSV type 1 (HSV-1) infection and 491 million people aged 15-49 had HSV type 2 (HSV-2) infection[2,3].

Genital HSV infections are a global public health problem, associated with important psychological and physical morbidity. In the last decades, genital herpes (GH) has been documented as the leading cause of genital ulcer in the sexually active population and one of the most common sexually transmitted infections (STI) worldwide[2,4]. The HSV can be transmitted via direct contact in sexual intercourse, during clinical evident episodes, or asymptomatic viral shedding. Many infections are subclinical, resulting in an underestimation of the prevalence of GH[4,5]. Primoinfection (infection in an individual without pre-existing antibodies to HSV-1 or HSV-2) and non-primary initial GH, that is, infection with one type of HSV in an individual who already has antibodies against the other type, manifest usually 4-7 days after contact, as multiple, mostly bilateral, mucocutaneous vesicles and erosions in the anogenital area[6]. These lesions are frequently associated with local pain, dysuria, and lymphadenopathy. A prodromic phase characterized by systemic symptoms such as fever, malaise, headache, and myalgia, and local burning or itching can precede the lesions[4,7]. By staying latent in the sacral sensory ganglia, the virus can reactivate and cause recurrent infections. In subsequent episodes, local and systemic symptoms are usually less severe and resolve more rapidly than in initial infections. A clinical diagnosis of GH should be laboratory-confirmed, with polymerase chain reaction (PCR) assays being the most sensitive and specific method to detect HSV-1 or HSV-2 DNA in specimens from mucocutaneous lesions. Type-specific antibodies, with a mean time to seroconversion of 3-4 weeks following an initial infection, distinguish primoinfection and non-primary initial GH from recurrent episodes and allow for diagnosis when other methods yield negative results[1]. Classically, HSV-1 has been mainly associated with orolabial infections and HSV-2 with genital ones. Although the clinical presentation of genital HSV-1 and HSV-2 infections are somewhat similar, their natural history and long-term prognosis are markedly different[8,9]. Infections resulting from HSV-1 produce fewer and milder symptomatic recurrences, and the incidence of viral shedding is much less frequent. Therefore, patients with HSV-1 GH can generally be expected to have a better prognosis and present a lower risk of transmission to sexual partners. On the other hand, HSV-2 infection is associated with more frequent recurrences, traduced in a higher risk of transmission[6,10,11]. Several studies published in recent years demonstrate a change in the epidemiology of GH, with an increasing proportion of infections caused by HSV-1[7,12-15]. This retrospective study conducted in a tertiary center in Lisbon aims to analyze and compare the epidemiological characteristics of patients with GH.

Methods

The STI clinic of the Dermatology and Venereology Department at Centro Hospitalar Universitário de Lisboa Central (CHULC) has provided venereologic services for many years. Patients may seek the clinic for screening, medical observation, and treatment of STI, without a referral and free of charge.

A retrospective and observational study was conducted to characterize the GH population in our center from January 2017 to December 2021. The results retrieved from the swabs collected for HSV infection diagnosis within this period were reviewed. The samples were collected by sterile cotton swabs of suspicious mucocutaneous lesions, that is, painful, most frequently grouped vesicles, vesicopustules, erosions

and/or ulcerations with underlying erythema. The collected samples were screened at the CHULC laboratory of molecular biology for HSV-1 and HSV-2 by real-time PCR using QuantStudio™ 5 Real-Time PCR system. From all samples yielding a positive result for HSV, only specimens collected from anogenital sites were included in our analysis. If multiple samples were collected from a given patient, only an isolate corresponding to the initial laboratory diagnosis was included in the dataset. Medical records of included patients were reviewed and their demographic data (age, gender, and nationality), sexual behavior, stage of infection (initial or recurrence), and clinical information (HIV and immune status, previous and co-STI – screening carried out if no recent screening, < 1 month) was retrieved and analyzed. The primary and non-primary initial infection was defined without use of serological tests, based on the patient's self-reported GH history and clinically presentation. Multiple scattered, bilateral, and painful lesions, tender lymphadenopathies, and systemic symptoms were considered indicators of initial GH (encompasses both primoinfection and non-primary initial infection).

Data collection and analysis were performed using Microsoft Excel 2021 and IBM SPSS version 24, respectively. Independent samples t-test was used to test differences between continuous and categorical variables at a significance level of 0.05. Non-parametric Mann-Whitney U-test was employed to evaluate differences when ordinal variables were addressed, at a significance level of 0.05. Fischer's exact test was used to test differences between two categorical variables at a significance level of 0.05, two-tailed.

Results

From January 2017 to December 2021, 11,309 patients were observed at our clinic. Of these, 239 (2.1%) had a laboratory-confirmed diagnosis of GH. HSV-2 was detected in 76.6% (n = 183) of the patients and HSV-1 in 23.4% (n = 56). The total number of GH diagnosed remained relatively stable throughout the years, with a decreasing proportion of HSV-1 infections. Analyzing the ratio of HSV-1 or HSV-2/GH infections, HSV-1 genital infections ranged from the minimum value of 16.3% (2021) to the maximum of 30% (2017), while HSV-2 infections ranged from 70% (2017) to 83.7% (2021). The clinic-epidemiological data collected are summarized in table 1, distributed accordingly to HSV type.

Demographic data

About two-thirds (68%; n = 163) of the subjects were men, with a mean age of 35.7 years (range: 17-87). The majority (60.2%; n = 144) of the patients were Portuguese. The proportion of men was higher in patients with HSV-2 (70.5%; n = 129) than with HSV-1 (60.7%; n = 34), (p = 0.169). The mean age was significantly lower in patients with HSV-1 (28.6 years; range: 17-63) than with HSV-2 (37.9 years; range: 19-87), (p < 0.001).

Sexual behavior

Regarding sexual orientation, 41% (n = 97) were men who have sex with men (MSM) or with men and women (MSMW), 31.4% (n = 75) were women who have sex with men, and 26.4% (n = 63) were MSW. In four patients, data concerning sexual orientation was not available in medical records.

Status of infection

About 39% (n = 95) of the patients sought medical observation for initial GH, this proportion being significantly higher in patients with HSV-1 (67.8%; n = 38) compared to patients with HSV-2 (30%; n = 55), (p < 0.001). Regarding clinical presentation, no global differences were noted between HSV-1 and HSV-2 genital infections.

Clinical data

Human immunodeficiency virus (HIV) infection was found in 17.6% (n = 42) of all patients, with two *de novo* diagnoses. It was significantly more prevalent among men (n = 39; 24.2%; p < 0.001), MSM/MSMW (n = 34; 35.1%; p < 0.001) and within the HSV-2 group (n = 38; 20.8%; p = 0.018). Other causes of immunosuppression such as neoplasms, end-stage kidney disease, or receiving a solid organ transplant were identified in 5% (n = 12) of the subjects.

Screening for other STI (gonorrhea, chlamydia, and syphilis) was performed in 182 of the patients. The prevalence of one or more coinfections was about 16% (n = 30), being statistically more prevalent within the group of MSM/MSMW (n = 22; 22.7%). The most common was anorectal chlamydia affecting 5.2% (n = 10), followed by anorectal gonorrhea (4.7%; n = 9).

Eighty-three patients (34.7%) had a previous diagnosis of gonorrhea, chlamydia, syphilis, and/or genital warts in

Table 1. Clinical and epidemiological characterization of GH cases, accordingly to HSV type

	HSV-1	HSV-2	Total	Statistical significance
Gender				0.169
Male	34	129	163	
Female	22	54	76	
Median age, years	28.6	37.9	36.9	< 0.001
Nationality				0.694
Portuguese	35	109	144	
Other	21	74	95	
Sexual behavior				0.591
MSW	13	50	63	
WSM	22	53	75	
MSM/MSMW	21	76	97	
NS	-	4	4	
Status of infection				< 0.001
Initial GH	38	55	95	
Recurrence	18	127	143	
NS	-	1	1	
HIV	4	38	42	0.018
Other immunosuppression	1	11	12	0.166
Concurrent STI (no. of patients affected)	7	23	30	0.719
Neisseria gonorrhoeae	2	11	13	
Chlamydia trachomatis	3	14	17	
Syphilis	2	2	4	
Previous STI (no. of patients affected)	15	68	83	0.146
Syphilis	6	39	45	
Gonorrhea	9	32	41	
Chlamydia	6	26	32	
Condyloma acuminatum	4	17	21	

GH: genital herpes; HIV: human immunodeficiency virus; HSV-1: herpes simplex virus type 1; HSV-2: herpes simplex virus type; MSM: men who have sex with men; MSMW: men who have sex with men and women; MSW: men who have sex with women; NS: not specified; STI: sexual transmitted infections; WSM: women who have sex with men.

the past. From these, the majority (82%; n = 68; p = 0.146) were diagnosed with HSV-2 GH and 77% (n = 64) were MSM/MSMW (p < 0.001). Forty-five subjects had at least one previous diagnosis of syphilis, 41 of gonorrhea, 32 of chlamydia, and 21 of *condyloma acuminatum*.

Discussion

In the last decades, the incidence of GH has increased worldwide, with an increasing proportion of HSV-1 as a causative agent in many developed countries[7,15]. In this study, HSV-2 was the main causative agent (76.6%). On the other hand, our results depicted a scenario where the proportion of HSV-1 diagnosis decreased throughout the study period, with a global prevalence of 23.4%. Interestingly, a high proportion of subjects (39.7%) in our study is from foreign countries, with a prevalence ranging from 6.7% to 8.8%. About a third of the individuals are from Asia, Africa, or America. From this last group, 87.5% had a diagnosis of GH caused by HSV-2, representing 34.4% of the HSV-2 population in the study, which aligns with a global HSV-2 seroprevalence study that observed the highest prevalence in Africa, followed by the American continent[16].

Overall and in each HSV type group, the rate of males was higher than females. Nevertheless, women represented 39% (n = 22) of the patients diagnosed with HSV-1, compared to 29.5% (n = 54) in the HSV-2 group. These data are in accordance with recently conducted studies, in which HSV-1 was most frequently isolated in young females[7,9,10,15]. For instance, in Finland, 63.6% of patients diagnosed HSV-1 GH between 2008 and 2012 were female[15].

We highlight that the mean age of patients with HSV-1 infection was significantly lower than of those with HSV-2 GH (28.6 and 37.9, respectively). Furthermore, the

proportion of patients that sought medical observation for initial GH was, proportionally, significantly higher among patients with HSV-1 (67.8%) compared to patients with HSV-2 (30%). An important fact to take into account is that genital HSV-1 infections are associated with less reactivation and clinical recurrences, with symptomatic episodes generally corresponding to initial infections[6,10,14]. An evolution toward a predominance of HSV-1 in younger people has been observed in recent studies[7,9,12,15,17]. Roberts et al. showed that HSV-1 became the most common cause of new genital HSV infections in a population of college students in Wisconsin[9]. Several factors can potentially explain the high proportion of GH in younger populations. Korr et al. pointed out the role of the decreased HSV-1 seroprevalence among children and adolescents due to improvement in hygiene and living conditions[18]. These susceptible younger populations, associated with earlier sexual debut, increased frequency of oral sex and can explain this epidemiological change in GH[1,4,7,9,12,14]. Finally, the use of condoms almost exclusively for vaginal and anal intercourse could reduce exposure to HSV-2 and consequence lower incidence in these population[9,10]. Reis et al. conducted a study to analyze trends in Portuguese adolescents' sexual behaviors, showing that the age of sexual initiation and sexual intercourse under the influence of alcohol or drugs decreased in Portugal between 2002 and 2014, while condom use increased[19].

Of note, in our study, both coinfections and history of previous STI were more frequent in patients with HSV-2 GH, with HIV infection being significantly more prevalent among this group (n = 38; 20.8%). Including HIV in the analysis, 44% of the subjects with HSV-2 had a history of previous STI, compared to 30% of the ones diagnosed with HSV-1 GH. Similar findings were observed in Spain, where Macho-Aizpurua et al. found that gonorrhea was significantly associated with GH caused by HSV-2[7,10]. Mathew et al. reported that about 79% of patients with HSV-2 infection have multiple sexual partners, a known risk factor for acquiring multiple STI[13]. Furthermore, HSV-2 infection has also been associated to a 3-fold increased risk of acquiring HIV[20]. As coinfections were statistically more prevalent within the MSM/MSMW group in our study, 41.5% of patients with HSV-2 being part of this group may constitute a confounding factor in the established association between HSV-2 and coinfections.

We recognize the limitations of our observational and retrospective study, as the data collected from a single STI center in Lisbon may not be representative at a population level. The decreasing prevalence of HSV-1 infections found over the period studied may be biased by these confounding factors. Furthermore, investigator interpretation and self-reporting bias may have occurred, since the initial episode was defined by clinical presentation and self-reported GH history registered in medical records.

Conclusion

To the best of our knowledge, no comparable studies on the clinical and epidemiological characterization of GH have been developed in Portugal. In our study, HSV-2 remained the most common cause of GH; however, HSV-1 tended to affect younger people and the proportion on initial GH was significantly higher in this group. These epidemiological particularities could have implications in clinical practice, as the natural history of HSV-1 and HSV-2, as discussed previously, is markedly different. Thus, counseling messages should emphasize the chronic character of GH and the possibility of transmission during subclinical shedding, pointing out that oral sex poses an increased risk of HSV-1 GH. Continuous attentive surveillance and systematic testing are essential to deepen our knowledge about the epidemiology of genital HSV infection.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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