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First confirmed Lymphogranuloma venereum (LGV) cases among MSM in Bulgaria, 2020–2021

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Abstract

Although the spread of Lymphogranuloma venereum (LGV) among European men who have sex with men (MSM) has been endemic since 2003, to the author's knowledge no LGV cases have been confirmed in Bulgaria up to date and treatment in suspected LGV patients has been presumptive due to lack of diagnostic capacity. The objective of the study was to genotype *C. trachomatis*-positive samples from attendees of a sexual health center in Sofia from 2020-2021 in order to be able to detect LGV circulation among MSM in Bulgaria. During the study period, a total of 246 MSM were tested with commercially available nucleic acid amplification tests (NAATs) to detect *C. trachomatis* in first void urine (FVU), pharyngeal and rectal swabs. Thirty-one consecutive clinical samples found positive for *C. trachomatis* during diagnostic testing were retrospectively analyzed for the presence of *C. trachomatis* serovars L1-L3. LGV genovars-specific *C. trachomatis* DNA was detected by *pmpH* PCR from the same specimen. LGV genovars were confirmed with partial *ompA* gene sequencing. Altogether 31 *C. trachomatis*-positive samples (22 FVU, 1 pharyngeal and 8 rectal swabs) were successfully typed by *pmpH* PCR. Twenty-nine samples contained non-LGV and two samples LGV *C. trachomatis* types. All the LGV types were found in rectal samples. Detected L types were confirmed to be serovar L2 with *ompA* sequencing. The data show that LGV circulate also among Bulgarian MSM, which underscores the importance of expanding LGV testing capacity in order to better inform patient management. Enhanced surveillance and genotyping programs could help measure and monitor LGV prevalence in Bulgaria.

Keywords: Lymphogranuloma Venereum; LGV; MSM; Bulgaria

1. Introduction

Lymphogranuloma venereum (LGV) is an infection caused by invasive serovars of *Chlamydia trachomatis* (L1, L2 or L3). Classically, LGV is characterized by the development of transient genital ulcers, followed by the appearance of tender unilateral inguinal and femoral lymphadenopathy. If left untreated, the infection may lead to long-term complications such as deep tissue abscess formation, strictures, fissures, and chronic pain [1]. Over the past decades the classical inguinal presentation has become increasingly infrequent, with proctitis and proctocolitis now the most commonly reported clinical manifestations of LGV [2]. Anorectal ulcerations, haemopurulent discharge and bleeding, tenesmus, and lower abdominal cramping and pain are the primary clinical features, and persistent infection can lead to the development of perirectal abscesses, fissures, and systemic symptoms such as fever, malaise, weight loss, and fatigue. LGV proctitis and proctocolitis has been established as endemic among men who have sex with men (MSM) in large metropolitan areas in Europe, North America and Australia [3]. However, the situation across Europe is unclear with the majority of LGV cases notified in just three countries (the United Kingdom, Netherlands and France) and sparse or absent data from most other European countries, including Bulgaria, due to limited testing capacity [4]. The lack of appropriate diagnostics not only restricts surveillance data but also has a direct negative impact on patient

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management. LGV proctitis and proctocolitis can be difficult to distinguish from inflammatory bowel diseases [5] that could lead to missed LGV infections. A correct diagnosis of LGV is essential to prevent severe complications and to ensure appropriate treatment, which is currently of a longer duration compared with non-LGV rectal *C. trachomatis* [6].

The objective of this study was to genotype *C. trachomatis*-positive samples from attendees of a sexual health center in Sofia from 2020-2021 in order to be able to detect LGV circulation among MSM in Bulgaria.

2. Material and methods

2.1. Patient management and LGV treatment

The Center for Sexual Health "CheckPointSofia" was established by the Doctors without Borders mission and has been engaged in voluntary and confidential HIV testing and counseling for over 20 years. Since it is a LGBT friendly environment, more than 75% of yearly male consultations involve MSM. In addition to a behavioral risk assessment, MSM attending CheckPointSofia are offered nucleic acid amplification tests (NAATs) for *C. trachomatis* and *Neisseria gonorrhoeae* from first void urine (FVU), pharyngeal and rectal samples. The samples are routinely referred to the National Center of Infectious and Parasitic Diseases (NCIPD), where molecular diagnostics are performed (AmpliSens for detection of Chlamydia trachomatis-FRT and Neisseria gonorrhoeae-screen-FRT). Detected *C. trachomatis*-positive cases with urogenital infection are treated at CheckPointSofia with the recommended regimen of 100 mg doxycycline twice daily for seven days, regardless of presence/absence of symptoms [7]. Cases with extragenital chlamydial infection are placed on extended doxycycline treatment (≥14 days), lasting 14 days in asymptomatic/mild cases and up to 21 days in cases with severe signs of proctitis, as recommended if no LGV diagnostic test is timely available [6]. In case of *C. trachomatis* and *N. gonorrhoeae* co-infection the antimicrobial treatment is initiated with ceftriaxone 500 mg IM plus azithromycin 2 g orally and continued with doxycycline. Test of cure (TOC) for *C. trachomatis* is performed ≥21 days post-treatment. Contact tracing is conducted for all cases and sexual contacts and partners were encouraged to visit CheckPointSofia for testing.

2.2. Laboratory confirmation of LGV cases

Irrespective of site of infection, HIV status and the presence of symptoms, all DNA extracts found positive for *C. trachomatis* during diagnostic testing from 2020 to 2021 from MSM were stored at -79^{0}C at NCIPD for further analysis. As soon as LGV diagnostics became available at NCIPD in January 2022, the preserved samples were retrospectively analyzed for the presence of *C. trachomatis* serovars L1-L3. LGV genovars-specific *C. trachomatis* DNA was detected by real-time PCR, targeting a 36-base pair (bp) deletion region of the polymorphic membrane protein H gene (*pmpH*) that could differentiate non-LGV and LGV strains, as described previously [8]. Detected LGV genovars were then confirmed with partial *ompA* gene sequencing, as previously reported [9].

3. Results

During 2020-2021 over 2240 MSM consultations were conducted at CheckPointSofia and samples from 246 MSM (median age 30 years, range 16–50) were referred for *C. trachomatis* and *N. gonorrhoeae* testing at NCIPD, leading to the confirmation of 31 *C. trachomatis* cases (Table 1). Among cases, 19 had no symptoms (13 urogenital, 5 rectal and 1 pharyngeal infections), and 12 were symptomatic (7 urogenital and 5 rectal infections). Two of the symptomatic rectal *C. trachomatis* cases had mild symptoms (i.e. local discomfort) and the other three cases presented with severe symptoms of anorectal pain, tenesmus and haemopurulent discharge and bleeding per rectum. All *C. trachomatis*-positive cases were effectively treated with negative TOC ≥21 days post-treatment.

Table 1 Distribution of *C. trachomatis* diagnoses, symptoms and duration of therapy according to infection site

Infection site	Asymptomatic	Symptomatic	Doxycyline treatment
Urogenital	13	7	7 days
Rectal	5	5	14-21 days
Pharyngeal	1	-	14 days

Altogether 31 *C. trachomatis*-positive samples (20 FVU, 1 pharyngeal and 10 rectal swabs) were successfully typed by *pmpH* PCR. Twenty-nine samples contained non-LGV and two samples LGV types. Both detected LGV types were found in rectal samples from patients with severe proctitis. One case was MSM in the age group 20-24 and the other was in the group 25-34; one was HIV-positive and the other was HIV-negative with samples taken 18 months apart from each other. Detected L types had *ompA* sequences identical to that of reference strain L2/434/BU (GenBank accession no. AM884176.1).

4. Discussion

This retrospective study presents data from a first LGV investigation in Bulgaria after introduction of LGV diagnostics at NCIPD. LGV genotype *C. trachomatis* was identified in two out of ten tested rectal samples, taken over a year and a half apart, indicating that a direct epidemiological link between the two cases is highly unlikely. Even within this small sample size, these findings suggest underdiagnosis of LGV infection among MSM in Bulgaria, and unidentified chains of transmission.

The first confirmed cases of LGV infection in Bulgaria displayed similarities with cases previously identified among MSM in other European countries. Specifically, anorectal infection was the primarily infection site, and severe proctitis corresponded to what is typical for LGV proctitis [3]. In addition, L2b has been described as the most prevalent genovar of the ongoing LGV epidemics in Europe [2, 10], and detected LGV strains among MSM in Bulgaria revealed *ompA*-sequences similar to the L2/434 reference strain. This is in accordance with recent European studies where an evolution towards this genovar has been observed [11–13]. Although LGV outbreaks were initially characterized as affecting predominantly HIV-positive MSM [14], recent European studies have reported a rising trend of LGV among HIV-negative MSM [15–17]; which is consistent with our finding of both HIV-positive and HIV-negative LGV case. The recommended therapy for LGV proctitis is oral doxycycline, 100 mg orally twice daily for three weeks [6]. The LGV cases were treated presumptively with the recommended dose of doxycycline, but an additional 9 cases with extragenital chlamydial infections were also treated for a prolonged period of time. This extended regimen was chosen as LGV diagnostics were not available at the time samples were collected, and was only introduced in January 2022. Building up a laboratory capacity will help to suspend antibiotic overuse and thus enhance antimicrobial stewardship efforts.

A strong public health response to raise awareness of LGV among clinicians, laboratories and MSM in Bulgaria is needed. This study highlights the importance of laboratory capacity (at least at reference laboratory level) to conduct genotyping to identify serovars/genovar L1, L2 and L3 in *C. trachomatis*-positive samples in order to ensure rapid diagnosis and subsequent appropriate treatment. In addition, clinicians should maintain a high index of suspicion for LGV in MSM with rectal symptoms, irrespective of HIV-status or co-infections with other STIs. Sexual contacts of LGV cases should be traced and tested. Ultimately, continuous attentive surveillance and systematic testing are needed to deepen our knowledge about LGV epidemiology and reduce LGV burden among MSM.

The presented retrospective study was limited to a small number of cases from one consultation setting in Sofia. Nevertheless, this is the first study using LGV diagnostics in the country, and our findings suggest likely underascertainment of LGV among MSM in Bulgaria. LGV diagnostics are largely unavailable in the country, and, as evidenced by our study this can lead to suboptimal treatment choices and directly affect patient management.

5. Conclusion

This study documents LGV circulation and its likely underestimation among MSM in Bulgaria, which underscores the importance of expanding LGV testing capacity in order to better inform patient management. Moreover, enhanced surveillance and genotyping programs in Bulgaria could support a better understanding of LGV prevalence in the European region.

Compliance with ethical standards

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Disclosure of conflict of interest

None to declare.

Statement of ethical approval

The study was reviewed and approved by the institutional review board (IRB) 00006384.

Statement of informed consent

Written informed consent was obtained from all patients for personal data collection and microbiological sample testing.

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