

## COMMENTARY

## Updates on lymphogranuloma venereum

Lymphogranuloma venereum (LV) is a sexually transmitted infection (STI) caused by *Chlamydia trachomatis* (CT) genovars L1, L2, L3. Infection by these CT genotypes may result in more invasive disease compared to other genotypes (A–K), since L1–L3 strains have tropism not only for the epithelial surfaces but also for the lymphatic tissues. After an incubation period of 1–2 weeks, the infection manifests with painful small erosions or ulcers in the site of the sexual contact (genitals, anus, rectum, oropharynx) lasting for 2–3 days and followed by painful, often unilateral, regional lymphadenopathy. The inguinal/femoral lymph nodes may become tender and fluctuant (buboes) and may undergo necrosis. Their rupture occurs in 30% of cases. During this stage, systemic symptoms such as fever, headache, nausea, anorexia and myalgia may occur.

The tertiary stage of the disease, which does not necessarily follow the lymphadenopathy, results from the progressive spread of the infection with destruction of tissues in the involved areas: the lymph nodes rupture causes haemorrhage and friability of the anorectal mucosa with tenesmus and mucous–sanguineous rectal discharge. Later, as healing occurs, formation of strictures, fistulas and abscesses leads to the destruction of anal and rectal structures.<sup>1</sup>

The most commonly reported symptoms are anorectal pain, tenesmus, bleeding and mucous discharge (proctocolitis), indicating that the infection is mainly transmitted by anal sex. However, up to 25% of the patients are asymptomatic and LV diagnosis is missing.<sup>2</sup>

Diagnosis requires detection from the infected site of CT nucleic acid by polymerase chain reaction (PCR). Samples can be obtained from the ulcer base exudates, from rectal/genital tissue or by aspiration from fluctuant lymph nodes. The laboratory identification of CT L1–L3 genovars is crucial to diagnose LV correctly, but, regrettably, most laboratories do not have genetic tools to distinguish LV genotypes from other CT genotypes. Therefore, routine LV surveillance programme is inadequate even in high-income countries and LV confirmation by analysis of the *ompA* gene (encoding for the CT major outer membrane protein) on a CT positive sample is mainly performed for research purposes.<sup>1,2</sup>

Data on LV epidemiology showed that the disease is still endemic in Africa, Asia and South America. A recent study from Buenos Aires, Argentina, found that among the samples of men with CT proctitis, the majority (68.8%) were positive for L2

genotypes.<sup>3</sup> Previously considered rare in the Western Countries, an outbreak in the Netherlands in 2003 brought LV attention and more cases are now being reported in Europe as well as other high-income countries, especially among human immunodeficiency virus (HIV)-infected men who have sex with men (MSM).

In this journal, Neves *et al.* carefully analysed the LV prevalence in Lisbon, Portugal. The samples collected for CT and *Neisseria gonorrhoeae* (NG) testing (rectal, cervical, urethral, pharyngeal swabs and urine) between 2016 and 2019 were reviewed, and those with CT positive results were further analysed for *ompA*-genotyping. Just over 10% of the CT positive samples corresponded to LV-associated strains with an increasing number of diagnosis over the years. Most of the LV positive samples were anal swabs (90%) of HIV-positive MSM with symptoms of moderate–severe proctitis (mucopurulent discharge, tenesmus, pain, rectal haemorrhage). The most commonly detected genotype was L2/434 (67%), followed by L2b (21%),<sup>4</sup> in line with other recent European studies which found the variants of L2 as the predominant genovars.<sup>5,6</sup>

Similarly, in a recent French study LV-positive samples were detected in 18.7% of anorectal CT-positive specimens from MSM and the genovar L2 was the most prevalent.<sup>7</sup> In Italy, LV prevalence in CT-positive anorectal samples from MSM was lower (4%) compared to the Portuguese and France prevalence and the genovars L2f, L2b and L2-L2b/D-Da were detected most commonly.<sup>5</sup>

Like in Europe, in USA, LV-associated genovars were detected in 14% of the CT-positive anorectal samples collected from seven public health laboratories between 2015 and 2018. All LV strains, detected in MSM, belonged to the genovar L2, mainly L2b and L2c variants. Notably, in this study, two novel L2 variants have been described (L2NV1 and L2NV2) but, unfortunately, data on the clinical features associated with these variants have not been collected.<sup>8</sup>

Very different reports come from China: several studies investigating the CT genotypes in CT positive anorectal swab of MSM reported that the most prevalent genotypes were G and D, while LV-associated genotypes were not found.<sup>9,10</sup> In Australia, as well, LV is very rare.<sup>11</sup> These data may be explained with fewer sexual intercourses with subjects belonging to different communities among MSM in China and Australia compared to the Western countries and/or with the different pathobiology of the various genovars and their ability to adapt to the environment.

Although the clinical features associated with CT genotypes have not always been described in detail, in most studies, the

presence and the type of symptoms did not differ with regard to the different LV-associated genovariants.<sup>4–6</sup> Only Rodríguez-Dominiguez *et al.*<sup>12</sup> reported less severe symptoms or no symptoms at all in patients infected by CT L2/L2f strain than in those infected by L2b strain (presenting bleeding and pain more frequently). However, concomitant infection by *N. gonorrhoeae* has been commonly found in LV case series, being a confounding factor in the analysis of LV symptoms.<sup>4–6</sup>


We think that a genotyping system for CT should be introduced as a routine test in laboratories dealing with sexually transmitted infections for two main reasons. Firstly, it would be useful to predict specific clinical features and outcomes of an infection characterized by different CT genovariants, like it would be recommendable in syphilis, another disease with proctean manifestations, to detect and isolate genovariants of *Treponema pallidum* with high capacity of neuroinvasion.<sup>13</sup> Lastly, CT genotyping could help to implement the active surveillance programmes of LV and also to guide clinicians in the disease management, not least in the therapeutic decisions. Indeed, according to the Center for Disease Control (CDC) guidelines, acute proctitis caused by non-LV CT strains should be treated with oral doxycycline (100 mg every 12 h) for 1 week, while LV proctitis requires a prolonged therapy for at least three weeks. The same treatment for LV in HIV-negative and HIV-positive patients is recommended.<sup>1,2</sup>

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G. Ciccarese,<sup>1,\*</sup>  F. Drago,<sup>1,2</sup> A. Rebora,<sup>2</sup> A. Parodi<sup>1,2</sup>

<sup>1</sup>Dermatology Unit, Ospedale Policlinico San Martino, Genoa, Italy,

<sup>2</sup>Di.S.Sal., Section of Dermatology, University of Genoa, Genoa, Italy

\*Correspondence: G. Ciccarese. E-mail: giuliaciccarese@libero.it

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