Jarisch-Herxheimer Reaction in Patients With Syphilis With or Without Prior Antibiotic Prophylaxis

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Samuel Lazzarin[1], Andrea Poloni[1], Giorgia Carrozzo[1], Giacomo Pozza[1], Chiara Fusetti[1], Francesco Caruso[1], Serena Reato[1], Maddalena Matone[1], Andrea Giacomelli[1], Maria V. Cossu[1], Andrea Gori[1], Giuliano Rizzardini[1], Spinello Antinori[1] and Davide Moschese[1]

[1]Department of Infectious Diseases, Luigi Sacco University Hospital, Milan (Italy)

BACKGROUND

Jarisch-Herxheimer reaction (JHR) is a transient clinical phenomenon that may occur within 24 hours after penicillin or other treponemicidal treatment in individuals with syphilis infection.

A punctual estimate of the actual frequency of this clinical condition is difficult to be determined because of many factors: variable and unstandardized diagnostic criteria, different methods used to investigate for signs and symptoms and heterogeneity in study populations. However, available evidence shows that JHR incidence ranges from 9 to 31%, reaching 56% in early syphilis when proactively investigated [1-3].

Aim of our study is to determine the incidence of proactively investigated JHR in individuals with or without prior antibiotic prophylaxis.

METHODS

We enrolled consecutive patients diagnosed with syphilis from April to September 2023 undergoing penicillin treatment.

Twenty-four hours after receiving the first penicillin dose, a phone call was made by a healthcare professional to assess the occurrence of JHR-related symptoms and the exposure to antibiotics (active against *Treponema pallidum*) before penicillin administration.

JHR was defined, after excluding other possible causes, by the presence of at least one of: fever, chills, new or worsening rash, headache and myalgia.

Individuals were categorized as exposed or not to antibiotics before penicillin if they received at least a 48-hours course of antibiotics in the 7 days before the first penicillin dose.

Antibiotic prophylaxis may help reducing the incidence of **Jarisch-Herxheimer reaction** after penicillin treatment

RESULTS

Ninety-five individuals were enrolled, with a median age of 41 years (IQR 33-50), including 93 (98%) males and 78 (82%) people living with HIV, of whom 61 (78%) with an HIV-RNA <50 cp/mL. Seventy patients (74%) were MSM, 14 (15%) transgender women and 11 (11%) heterosexuals.

The distribution of syphilis stages was: 5% primary, 12% secondary, 41% early latent, 41% late latent and 1% neurosyphilis. Previous penicillin treatment was reported in 50 patients (53%). Median RPR titer at diagnosis was 1:8 (IQR 1:2-1:16).

We identified 71 patients (75%) with a study-defined antibiotic exposure: 67 (94%) amoxicillin and 4 (6%) doxycycline. The median cumulative dose of amoxicillin was 9.5 g (IQR 6-12 g) and doxycycline 1200 mg (IQR 950-1400 mg).

Six patients [incidence 6.3% (95% CI 2.3-13.7%)] developed JHR, with fever being the most common clinical manifestation (4 in the antibiotic exposed and 2 in the antibiotic unexposed group). Among the subset of 55 patients with early syphilis (58%), 4 [incidence 7.3% (95% CI 1.1-10.2%)] had JHR (2 in the antibiotic exposed and 2 in the antibiotic unexposed group).

CONCLUSIONS

We observed a lower incidence of Jarisch-Herxheimer reaction (6.3%) when compared to previous studies [1,2]. This difference was even greater when the analysis was restricted to the early syphilis group, which is known to be the most prone to JHR [2]. Tsai et al showed that JHR occurred in 56% of patients with early syphilis after penicillin treatment [3], while JHR incidence was only 7.3% in our subset of patients with early syphilis. Moreover, our study included an higher proportion of patients with early syphilis than a previous work, which unexpectedly found an higher overall incidence of JHR (31.5%) [2].

Since most patients in our study was given amoxicillin or doxycycline prior to penicillin treatment, we can speculate that the observed lower incidence of JHR could be attributable to antibiotic prophylaxis. Although, a relatively low RPR titer in our study population may contribute to explain this finding. Other studies with larger sample size are needed to clarify if antibiotic prophylaxis could become an effective prevention strategy.

ADDITIONAL RESOURCES

1. Miller WM, Gorini F, Botelho G, et al. Jarisch-Herxheimer reaction among syphilis patients in Rio de Janeiro, Brazil. *Int J STD AIDS*. 2010;21(12):806-809.
2. Yang CJ, Lee NY, Lin YH, et al. Jarisch-Herxheimer reaction after penicillin therapy among patients with syphilis in the era of the HIV infection epidemic: incidence and risk factors. *Clin Infect Dis*. 2010;51(8):976-979.
3. Tsai MS, Yang CJ, Lee NY, et al. Jarisch-Herxheimer reaction among HIV-positive patients with early syphilis: azithromycin versus benzathine penicillin G therapy. *J Int AIDS Soc*. 2014;17(1):18993.

AUTHOR CONTACT INFORMATION

Institutional mail address: samuel.lazzarin@unimi.it