Jarisch-Herxheimer reaction

Description

This systemic reaction, also known as the Herxheimer's reaction, was classically described in the treatment of syphilis. It is believed to be caused by the release of endotoxin-like substances when large numbers of *Treponema pallidum* are killed by antibiotics.

It has been documented in tick-borne diseases like Lyme disease [1] , leptospirosis [2] and relapsing fever [3] , all of which are spirochaetal organisms. Candidiasis treated with systemic fluconazole has also been reported as causative [4] . The mechanism may not be straightforward as it is not a feature of neonatal syphilis or non-venereal syphilis in childhood. The reaction can be expected in 50-75% of primary or secondary syphilis, and in 16% of early latent infection but is very rare in late syphilis. It has been suggested that it is more severe in patients with HIV [5] [6] .

Epidemiology

The frequency of Jarisch-Herxheimer reaction according to age and sex is not yet known. The occurrence of Jarisch in syphilis is as follows [7] :

- Seronegative primary syphilis (55%)
- Seropositive primary syphilis (95%)
- Secondary syphilis (95%)
- Latent and late syphilis - not seen
- Lyme disease (7-30%)
- Leptospirosis (9%)

Presentation

- The reaction starts between 1 and 12 hours after the first injection of antibiotics and lasts for a few hours or up to a day.
- It is not seen with subsequent treatment.
- There is malaise, slight-to-moderate pyrexia, a flush due to vasodilation, tachycardia and leukocytosis.
- Any existing skin lesions become more prominent.
- Hyperventilation and tachycardia are accompanied by hypertension and then by a drop in blood pressure due to vasodilation and declining peripheral resistance.
- In some patients with early syphilis, a secondary rash may become visible which was absent before treatment.
- Usually, the reaction resolves over a period of 6-12 hours.

Differential diagnosis

It is important to recognise the reaction for what it is and not to ascribe it to a sensitivity to the antibiotic. Rarely, syphilis may be suspected by the appearance of the febrile reaction of the Jarisch-Herxheimer, perhaps with a fleeting rash, when treating another infection such as gonorrhoea. It is important to recognise this and to make the diagnosis and give an adequate course for syphilis.

Investigations

Usually no investigation is required but if an unexpected reaction to antibiotic treatment occurs then serological tests for syphilis are required.

Associated diseases

Although traditionally associated with syphilis, the reaction is also well documented with Lyme disease and relapsing fever.

For many years there has been a suggestion that mycoplasma may be involved in the aetiology of rheumatoid arthritis and other autoimmune diseases, including sarcoidosis. *Propionibacterium acnes* has been identified as a possible causative organism in sarcoidosis[8] . The Jarisch-Herxheimer reaction sometimes occurs after antibiotic treatment and the severity of the reaction is taken as evidence that the treatment is working[9] .

Management[5]

No treatment is usually required for the reaction per se, which is self-limiting and often resolves within 24 hours.

Treatment of severe leptospirosis-related Jarisch-Herxheimer reaction with fluid infusion, vasopressors, corticosteroids, inotropic support and transient dialysis has been reported[10] .

Prevention

Various measures can be taken to reduce the risk of the reaction or ameliorate its effects.

Judicious selection of antibiotics with a lower risk of Jarisch-Herxheimer reaction is helpful if the clinical situation allows it - eg, azithromycin therapy in HIV-positive patients with early syphilis[5] .

It is customary to give corticosteroids in late symptomatic syphilis, starting a day before the first penicillin injection and tailing it off the day after the first injection. A dose of around 30 mg prednisolone is typical. This does not prevent the Jarisch-Herxheimer reaction but is said to ameliorate it[11] . One study showed that treatment with anti-TNF-alpha Fab antibody fragments reduced the frequency of the Jarisch-Herxheimer reaction from 90-50%. Anti-TNF-alpha-treated patients had significantly lower increases in temperature, pulse rate and systolic blood pressure and lower plasma concentrations of interleukin 6 and 8 after treatment with penicillin[12] .

In pregnancy the incidence of the reaction when treating syphilis is about 40%[13] . Fetal monitoring should be performed, as similar proportions of patients develop regular uterine contractions and recurrent variable decelerations[14] . A review of the literature found conflicting evidence that the reaction is caused by release of endotoxin-like material from the spirochete as well as cytokine elevation in the body. The type of drug and the rate of clearance of the spirochetes have little effect on the incidence of the reaction. Many pre-treatment options have been explored with limited efficacy with the exception of anti-TNF antibodies [15] .

Complications

In early syphilis the reaction is only a minor nuisance. In late syphilis it can, on very rare occasions, be more serious. Thus, in neurosyphilis it may lead to epilepsy[16] or a rapid, irreversible progression and in general paresis it can cause exacerbation amounting to temporary psychosis. Sudden death has been reported in cardiovascular syphilis. In laryngeal gumma, local oedema may necessitate tracheotomy. In the later stages of pregnancy fetal monitoring is advised.

Prognosis

Recovery is usually swift and the course of treatment is completed.

Historical aspects

Adolf Jarisch (1850-1902) was an Austrian dermatologist. Jarisch published his description of the Jarisch-Herxheimer reaction in 1895, seven years before Herxheimer published his own description. As this was many years before the discovery of penicillin, the original description related to the treatment with mercury.

Karl Herxheimer (1861-1942) was a German dermatologist. Herxheimer published his description of the Jarisch-Herxheimer reaction in 1902. He had already resigned his positions because of his age when the Nazis took power in 1933 but, despite being Jewish, he stubbornly refused to leave his native country. He was imprisoned in the autumn of 1941 and on August 27 1942, aged 81, he died in a concentration camp.

Further reading

- McKenzie C, Olges J; Jarisch-Herxheimer Reaction After Cephalosporin Administration in Syphilis. Cureus. 2021 Jan 17;13(1):e12750. doi: 10.7759/cureus.12750.
- Guerrier G, Lefevre P, Chouvin C, et al; Jarisch-Herxheimer Reaction Among Patients with Leptospirosis: Incidence and Risk Factors. Am J Trop Med Hyg. 2017 Apr;96(4):791-794. doi: 10.4269/ajtmh.16-0457. Epub 2017 Jan 23.

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