An Atypical Presentation of Jarisch-Herxheimer Reaction In A Neurosyphilis Patient

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Introduction

The incidence of syphilis has increased in the US every year since 2000, reaching 9.5 cases per 100,000 persons in 2017. The prevalence of neurosyphilis among patients with early syphilis was **1.8%,** and was estimated to occur twice as often in patients with HIV infection as in those without HIV infection.

Jarisch-Herxheimer reaction (JHR) occurs within 24 hours of a patient receiving antibiotic treatment for a spirochetal infection, such as syphilis, Lyme disease, leptospira, or relapsing fever.

Patients **typically** experience:

- Shaking chills, a rise in temperature, exacerbation of existing skin rashes with symptoms resolving within a few hours.

The pathogenesis of JHR is often misunderstood as a cytokine-mediated inflammatory response to the release of toxins by dying spirochetes. However, this mechanism is likely incorrect, as it takes more than 48 hours for spirochetes exposed to antibiotics to die, and intact spirochetes can still be found in phagocytic vacuoles hours after treatment.

In *Treponema pallidum* infection, it is more likely that the administration of antibiotics alters the microbial surface of the spirochetes, exposing sites for antigen binding by antibodies and complement. These surface changes render the spirochetes more susceptible to phagocytosis by macrophages. In turn, the macrophages are stimulated by lipoproteins on the surface of the spirochetes to produce tumor necrosis factor (TNF) and trigger a broad inflammatory response.

Atypical findings of JHR:

- Meningitis, respiratory distress, renal/hepatic dysfunction, altered mental status, stroke and seizure.

In this case report, patient had a generalized tonic-clonic seizure after administering penicillin from an incidental finding of syphilis

The frequency of JHR in patients with primary, secondary, or early latent syphilis and an RPR titer greater than 1:32 is 41% when treated with penicillin, compared to 16% in patients with a titer less than 1:32. HIV-positive patients experienced the reaction 35% of the time, compared to 25% in HIV-negative patients.

Case Report

- Our patient is a 63 year old male who presented to the ER with severe back pain and was found to have a dissecting abdominal aortic aneurysm. He was treated surgically with fenestrated endovascular repair and his condition stabilized. However, in the course of his workup, blood serum testing revealed a methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia, as well as newly discovered positive HIV-1 and syphilis infections (with history of resolved full-body rash).
- Three days following the surgery, the patient was treated with IV penicillin G for syphilis. 8 hours after administering penicillin, the patient was found to have a generalized tonic-clonic seizure which involved full-body shaking, eyes rolling back and urinary incontinence. He experienced at least three episodes with postictal state, each lasting about 30 seconds, Patient was intubated, and lorazepam was given with levetiracetam for seizure prophylaxis. Workup was negative for acute hemorrhage. 24-hour video EEG showed no further seizure activity but slow background indicative for encephalopathy. Over the next few days, the patient's encephalopathy resolved.
- VDRL-CSF came back negative, which did not suggest neuro-syphilis. However, patient was treated for neuro-syphilis based on his clinical findings and HIV co-infection.
- The patient was treated with IV penicillin for newly diagnosed and previously untreated syphilis, and 8 hours later experienced generalized tonic-clonic seizures (GCSE), raising suspicion for an atypical presentation of the Jarisch-Herxheimer reaction (JHR).

References

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Discussion

Several factors support patient had JHR:

- Firstly, CT obtained immediately after the event and MRI obtained three days later showed no evidence of intracerebral hemorrhage, tumor, infection, or stroke.
- Secondly, the patient had no significant identifiable risk factors for seizure other than recent surgery and general anesthesia 3 days prior. He had no previous history of seizure, took no medications known to lower the seizure threshold, and demonstrated no evidence of symptomatic neurosyphilis which might predispose to seizure.
- Thirdly, in typical JHR, symptoms peak at 8 hours following administration of IV penicillin, with resolution within a few hours. This timing correlates exactly with our patient's seizure event.
- Fourthly, patient is HIV-positive and had an RPR titer of 1:128, placing him in the higher risk group.

Literature: Four case reports of patients experiencing seizure as a manifestation of JHR. Three of these patients experienced non-convulsive status epilepticus. One case report described a patient with neurosyphilis who experienced generalized convulsive status epilepticus that was determined to be a JHR. EEG of this patient demonstrated periodic lateralized epileptiform discharges. In all four of these cases, the patients showed symptoms of paralytic dementia (general paresis), which is part of the neurosyphilis spectrum of symptoms and is associated with dementia, seizures, pyramidal signs, optic atrophy, and dysarthria.

JHR is often underdiagnosed, with its typical fever and rash being misidentified either as symptomatic of the underlying infection or as an allergic reaction to the antibiotic. Physicians should anticipate the possibility of JHR when administering penicillin for the first time to a patient with syphilis. Physicians should be aware of seizure as a rare presentation of the reaction. Patients who experience status epilepticus (defined as seizure lasting >5 minutes or two or more seizures with no return to baseline in between) should be treated with lorazepam and other anti-epileptic drugs (AED) as needed in order to break the seizures. These patients should be started on a prophylactic AED such as levetiracetam or topiramate for at least 6 months following the seizure.

A final word on our patient's case: a VDRL test was negative in the patient's CSF. However, up to 70% of HIV-positive patients with neurosyphilis may have a negative VDRL. Therefore, the decision was made to treat the patient for suspected neurosyphilis with an extended inpatient course of IV penicillin G. It may also be noted that the four previously-reported cases of seizure in JHR all occurred in patients with neurosyphilis, which may suggest that our patient's seizure was an early manifestation of neurosyphilis in our patient. We believe more studies should be conducted to better understand this atypical manifest in order to create a guideline for treatment plan.