Penicillin-Induced Jarisch–Herxheimer Reaction

Sharon See, Emilie K Scott, and Marc W Levin

OBJECTIVE: To report a case of Jarisch–Herxheimer reaction (JHR) in a patient with presumed neurosyphilis and HIV.

CASE SUMMARY: A 45-year-old HIV-positive man (CD4+ count 450 cells/mm³ and history of AIDS-defining illness) presented with JHR after an initial intravenous dose of penicillin G for presumed neurosyphilis. The patient described feeling cold with worsening headache and chills approximately one hour after infusion of the first dose of penicillin. On examination, rigors, shallow inspirations, and chills were noted. He was afebrile, tachycardic, and tachypneic and had an oxygen saturation of 94% while breathing room air. His symptoms resolved within 10 minutes. Initially, this reaction was thought to be a result of a drug allergy, but upon further review, we determined that it was JHR.

DISCUSSION: It is not uncommon to confuse drug allergy with JHR. An objective causality assessment suggests that the JHR in our patient was probably related to penicillin. JHR is a self-limiting condition that warrants the continuation of antibiotic treatment in syphilis patients.

CONCLUSIONS: JHR should be an anticipated reaction to early doses of antibiotic treatment for treponemal diseases, such as syphilis. Treatment of JHR is largely supportive, such as administering antipyretic and antiinflammatory agents. Antibiotic treatment should be continued.

KEY WORDS: Jarisch–Herxheimer reaction, neurosyphilis, penicillin G, syphilis.

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Jarisch–Herxheimer reactions (JHRs) have been identified in patients treated for spirochete diseases including louse-borne relapsing fever, Lyme disease, leptospirosis, yaws, and early and late syphilis. It was first identified in the 1500s as a result of mercury treatment for medieval syphilis. JHR can occur with many medications as long as the antitreponemal concentrations are sufficient. These medications can include tetracyclines, penicillins, bismuth, and sulfonamides.[1] In syphilis, disease symptoms worsen and are often mistaken for allergic reactions to the treatment medications. JHR is more prevalent during secondary syphilis (70–90%), but can occur in any stage. No recent data describe the incidence of JHR in neurosyphilis.[2] The last case report cited was in 2002.[3] We describe a patient who developed JHR after an initial dose of penicillin G for presumed neurosyphilis.

Case Report

A 45-year-old HIV-positive man (most recent CD4+ count 450 cells/mm³ one mo prior, CD4+ nadir of 3 cells/mm³ 5 y prior, *Pneumocystis jiroveci* pneumonia 5 y prior, antiretroviral therapy for 5 y) was seen by his primary care physician for reports of headache for one month and rash for 2 weeks. He described the headache as global and constant and not relieved by ibuprofen or acetaminophen. The rash began on his arms and trunk, then spread to his penis and scrotum. He described it as nonpruritic and not painful. He reported exposure to syphilis through sexual contact 5 months before admission with a person with known syphilis. His rapid plasma reagin titer just prior to admission was 1:32, and serum fluorescent treponemal antibody was positive. Based on these results and his clinical picture, his primary care physician referred him to the hospital for a lumbar puncture to rule out neurosyphilis.

The physical examination upon admission to the hospital showed multiple 1 to 2-mm erythematous papules on his arms, legs, chest, and forehead, along with several painless, 2 to 3-cm denuded shallow ulcerations on his penis and scrotum. A lumbar puncture showed 14 502 cells, including 14 500 red blood cells and 2 white blood cells. The cerebrospinal fluid (CSF) was grossly bloody, with a negative culture and a negative venereal disease research laboratory (VDRL). Results of a noncontrast computed tomography scan of the head were unremarkable.

He was diagnosed with secondary syphilis and possible neurosyphilis. Even though CSF VDRL was negative, he was started on treatment for neurosyphilis because, although CSF VDRL is highly specific for neurosyphilis, it is not highly sensitive for diagnosis of neurosyphilis.[4] In addition, HIV-positive patients with neurosyphilis may be at increased risk for neurologic complications.[4] He was started on treatment with intravenous penicillin G 4 million units every 4 hours. The patient began to describe feeling cold, with worsening headache and shaking body chills approximately one hour after the first dose of penicillin. On examination, he appeared pale, with rigorous chills and shallow inspirations. He was afebrile (T 36.8 °C), with HR 140 beats/min, RR 28 breaths/min, and oxygen saturation 94% while breathing room air. He was alert and oriented to person, place, and time, and he remembered why he was in the hospital. He had no change in his rash or signs of airway compromise. He was immediately given intravenous diphenhydramine 50 mg and 2 tablets of hydrocodone 5 mg/acetaminophen 500 mg due to the initial concern of drug allergy.

Approximately 10 minutes later, he reported an improvement in his headache. On examination, his shaking chills had resolved, and his respi-

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rations were no longer shallow. His HR decreased to 129 beats/min, his oral T was 37 °C, oxygen saturation was 96% while breathing room air, BP was 107/58 mm Hg, and his RR normalized to 20 breaths/min. Initially, panic disorder and penicillin allergy were included in the differential diagnosis; however, after review of the literature, we were convinced that his presentation was consistent with JHR. As a result, penicillin treatment was continued. He was closely monitored during the next dose of penicillin and was comfortable, with stable vital signs throughout his course of treatment. He was not premedicated with diphenhydramine for the rest of his treatment and his BP was stable, ranging from 104/56 to 128/77 mm Hg. His white blood cell count was stable (5.7×10^3 cells/mm^3 on hospital day 1 and 6.4×10^3 cells/mm^3 on hospital day 3). On hospital day 7, it was noted that his rash had improved, with no new lesions forming. His headache persisted throughout his hospital stay, but was relieved by nonsteroidal antiinflammatory medication. He was discharged home after completing a 10-day course of penicillin G for presumed neurosyphilis.

Discussion

JHR can occur as early as 2 hours after exposure to antibiotic therapy and usually resolves within 24 hours.[5] Initially, patients may develop fever with rigors, then later defervesce and become diaphoretic. Patients may experience headache, malaise, and myalgias. Additionally, the signs and symptoms of the treated disease may worsen. Existing syphilitic lesions may become more painful and rashes may become more inflamed. Patients may become hypertensive due to vasoconstriction in early treatment and then later become hypotensive due to decreased peripheral resistance.[6] In syphilis-related JHR, leukocytosis with an increase of neutrophils and decrease in lymphocytes has also been identified.[7] JHR is usually seen in the treatment of early syphilis, but can also occur in the treatment of late syphilis. Local swelling associated with JHR occurring in late syphilis can be dangerous if there is involvement in the coronary ostia, cranial nerves, or larynx.[5]

Several hypotheses exist regarding the pathogenesis of JHR. It was originally thought to be caused by release of endotoxin as treponemes are killed, but this theory has since been challenged. A study of 19 patients with secondary syphilis found no detectable endotoxin before, after, or during therapy in any of the 15 subjects who developed JHR.[8] Further, some have proposed that if endotoxin release were the true basis for JHR, then the amount of treponemes present should influence the severity of reaction. However, even patients with seronegative primary syphilis can experience reactions similar to those of patients with more progressive disease.[7]

Another widely held theory involves activation of the cytokine cascade, which occurs during destruction of spirochetes upon antitreponemal treatment. This has been specifically described in the treatment of relapsing fever with high doses of penicillin. Penicillin treatment makes spirochetes more susceptible to phagocytosis, which then stimulates the release of cytokines, including tumor necrosis factor (TNF) and interleukins-6 and 8. It has been proposed that the release of TNF occurs prior to any signs of fever. The activation of the inflammatory cascade manifests in the patient as rigors, fever, chills, tachypnea, tachycardia, and hypotension.[9] Not surprisingly, targeting these cytokines may be a reasonable approach to prevent JHR.

Treatment of JHR is largely supportive (ie, antipyretics).[4] No preventive treatments are currently available; however, attempts to blunt the cytokine response to antitreponemal treatment have shown some success. In a study of 49 patients with louse-borne, relapsing fever, anti-TNF-α was given immediately before 600 000 units of penicillin G procaine.[10] Half of the anti-TNF-α group experienced clinically evident reactions, compared with 90% of the control group ($p = 0.006$). Patients receiving anti-TNF-α also experienced lower elevations in blood pressure (15 vs 25 mm Hg; $p = 0.003$), temperature (0.8 vs 1.5 °C; $p < 0.001$), and heart rate (13 vs 31 beats/min; $p < 0.001$). These vital signs returned to normal more quickly than those in the control group.

Gudjonsson and Skog[11] conducted a study in 51 patients with early syphilis to determine the effect of prednisolone on JHR. Patients were administered aqueous procaine penicillin 10–20 units/kg to determine whether they were susceptible to JHR and then given a second dose of either 600 000 or 2.2 million units. The investigators gave patients prednisolone 20–60 mg the day before and on the same day as the second penicillin dose. Prednisolone prevented fevers in most of the treated patients, but did not improve the leukocyte pattern. Specifically, neutrophil counts continued to increase and lymphocyte counts continued to decrease, which is consistent with JHR presentation. The 2 patients who developed fevers received 20 and 40 mg of prednisolone, respectively. The authors reported that patients in the prednisolone-treated group had fewer focal reactions (4 vs 7); however, these reactions were not fully described and could have been highly variable.

If a patient does develop JHR, antibiotic treatment should be continued. The reaction should not be mistaken for an allergic drug reaction. Inappropriate discontinuation of syphilis treatment can be dangerous and can incorrectly label the patient with a drug allergy. Untreated disease can result in worsening of symptoms, cardiac and central nervous system involvement, and ultimately death.

Our patient exhibited classic signs of JHR including rigors, worsening of headache, chills, and tachycardia. Although fever is a common sign in JHR, it is not unusual for a neurosyphilis patient to be afebrile, as in our patient. The incidence of fever varies depending on the type of neurosyphilis. According to the literature, fever is more prevalent in patients with paresis (53–95%) than tabes dorsalis (9–23%) or other types (12–36%).[12] It is more common to see fever if patients have positive CSF findings including elevated cell counts, protein, and positive serum treponemal tests. The CSF in our patient was unhelpful for assessment since it was a traumatic puncture.

Conclusions

This case describes a typical presentation of JHR in a patient being treated for neurosyphilis. Although it was a typical presentation of JHR, it was initially thought to be an allergic reaction to penicillin. Due to the infrequency of syphilis cases in our unit, it was not surprising that the pre-

sentation was deemed to be an adverse drug reaction. Although the Naranjo probability scale[13] does not exactly apply to our case because it was not an adverse drug reaction, it indicates a probable relationship between penicillin G and the JHR. JHR must be an expected occurrence when treating any patient with syphilis or other treponemal diseases. The signs and symptoms of JHR should be anticipated and providers should properly educate the patient on this phenomenon. Most importantly, this case serves to remind practitioners that antibacterial therapy should be continued in these patients.

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EXTRACTO

OBJETIVO: Informar el caso de una reacción Jarisch–Herxheimer (JHR) que ocurrió en un hombre con infección con el HIV y sospecha de sífilis.

RESUMEN: Un hombre de 45 años de edad, infectado con HIV y con un contaje de células CD4 de 450 células/m³, desarrolló una reacción Jarisch–Herxheimer luego de la administración de la dosis inicial de penicillin G intravenosa para tratar una presunta neurosífilis. El paciente refirió dolor de cabeza, sensación de enfriamiento, y escalofríos aproximadamente una hora luego de la administración de la primera dosis de penicilina. Al examinar al paciente, se observó la presencia de rigor. El paciente estaba afebril, taquicárdico y taquipnéico y con saturación de oxígeno de 94%. Sus síntomas resolvieron dentro de un período de 10 minutos. Inicialmente, se pensó que la reacción había sido una reacción alérgica a penicilina, pero luego se determinó que esta era una reacción Jarisch–Herxheimer.

DISCUSIÓN: La reacción Jarisch–Herxheimer comúnmente se puede confundir con una alergia a penicilina. La evaluación de esta reacción sugiere que la reacción en este paciente fue probablemente debido a la penicilina. JHR es una condición auto limitante que amerita el que se continúe el uso del antibiótico para el tratamiento de la sífilis. Este artículo describe la presentación de un JHR en un paciente con una presunta neurosífilis, y se presenta una revisión de esta reacción.

CONCLUSIONES: JHR es una reacción que se debe anticipar luego de la dosis inicial del antibiótico en el tratamiento de infección por treponema pallidum, como lo es la sífilis. El tratamiento de JHR es primordialmente paliativo, e incluye el uso de antipiréticos y analgésicos. El tratamiento con antibióticos debe continuar.

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RÉSUMÉ

OBJECTIF: Rapporter un cas de réaction de Jarisch–Herxheimer chez un patient présumé atteint de neuro-syphilis et du VIH.

SOMMAIRE DU CAS: Un homme âgé de 45 ans atteint du VIH (CD4 de 450 cellules/mm³ et antécédents de maladie reliée au syndrome d'immunodéficience acquise) s'est présenté avec une réaction de Jarisch–Herxheimer, après une dose initiale de pénicilline G administrée par voie intraveineuse, pour une présumé neuro-syphilis. Le patient a décrit la réaction comme une sensation de froid avec maux de tête, allant en s'intensifiant, et frissons, approximativement une heure suivant l'infusion de la première dose de pénicilline. Des raideurs, inspirations superficielles, et frissons ont été notés à l'examen. Le patient était apyrétique, tachycardique, tachypnéique, et présentait une saturation à l'oxygène de 94% à l'air ambiant. Ces symptômes se sont résorbés à l'intérieur de 10 minutes. Au départ, cette réaction semblait similaire à une allergie au médicament, mais une réaction de Jarisch–Herxheimer a été démontrée, suite à une revue additionnelle du cas.

DISCUSSION: Il n'est pas rare de confondre une allergie au médicament avec une réaction de Jarisch–Herxheimer. Une évaluation objective du lien de causalité a démontré que la réaction de Jarisch–Herxheimer était probablement reliée à la pénicilline. La réaction de Jarisch–Herxheimer est une condition limitée dans le temps et justifie la poursuite de l'antibiothérapie chez les patients atteints de syphilis. Cet article décrit un cas typique d'une réaction de Jarisch–Herxheimer chez un patient présumé atteint de neuro-syphilis et offre une opportunité pour réviser cette réaction.

CONCLUSIONS: La réaction de Jarisch–Herxheimer devrait être une réaction anticipée aux premières doses d'antibiothérapie pour les tréponématoses telle que la syphilis. Le traitement de la réaction de Jarisch–Herxheimer est principalement de soutien, tel que l'administration d'agents antipyrétiques et anti-inflammatoires. L'antibiothérapie devrait être maintenue.

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