Elevated CSF Cytokines in the Jarisch-Herxheimer Reaction of General Paresis

Larry E. Davis, MD; Ryan Oyer, MD; J. David Beckham, MD; Kenneth L. Tyler, MD

IMPORTANCE The Jarisch-Herxheimer reaction (JHR) is a well-recognized transient worsening of signs and symptoms occurring soon after the first dose of an appropriate antibiotic for several spirochetal infections. The pathogenesis of this reaction is poorly understood. In this case study of cerebrospinal fluid (CSF) cytokines, we aimed to improve understanding of the pathogenesis of JHR in patients with neurosyphilis who develop transient neurologic signs.

OBSERVATIONS Four hours after receiving penicillin for general paresis, a 55-year-old man developed a severe JHR characterized by fever, tachycardia, hypertension, obtundation, seizures, and a neutrophilia lasting 18 hours. Cerebrospinal fluid obtained at the peak of the JHR demonstrated a switch from a mild lymphophilia to a moderate neutrophilia. He had markedly elevated CSF interleukin (IL) 8 and likely elevated IL-1β, IL-10, and IL-15 levels, which returned to normal in follow-up CSF examination results.

CONCLUSIONS AND RELEVANCE To our knowledge, this is the first report of elevated CSF cytokines in a patient with a JHR, which possibly contributed to the neurologic signs of JHR. Further studies on the innate inflammatory response during episodes of acute infection and inflammation are needed to develop targeted therapies to modulate this system, which could, in turn, improve future outcomes and modify the JHR.

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F or several spirochetal infections, the Jarisch-Herxheimer reaction (JHR) is a single episode of transient worsening of signs and symptoms occurring soon after the first dose of an appropriate antibiotic. The JHR was first described following treatment of syphilis with mercury compounds but has been described following treatment with penicillin, tetracycline, ceftriaxone, and other antibiotics. The JHR is most commonly recognized in spirochetal infections beginning hours after the patient is initially treated with appropriate antibiotics and is associated with infections due to many spirochetes including Treponema pallidum, louse-borne relapsing fever (Borrelia recurrentis), leptospirosis (Leptospira icterohaemorrhagiae and Leptospira interrogans), yaws (Treponema pallidum subspecies pertenue), and Lyme disease (Borrelia burgdorferi).

For infections of T pallidum, JHR most often develops in patients with secondary or primary syphilis and less often in all-type tertiary syphilis and syphilitic aortitis. The overall reported incidence of JHR in syphilitic patients, including general paresis, varies and is as high as 75% in older literature that required only a transient fever for the diagnosis. In more recent literature, the incidence is around 10%. Common clinical manifestations of patients with early syphilis include fever, chills, malaise, headache, myalgias, tachypnea, nausea, arthralgias, and worsening of syphilitic skin lesions. The onset of JHR typically begins around 2 hours after the initial dose of antibiotic, peaks from 4 to 8 hours, and subsides around 24 hours. In blood, there is typically a neutrophil leukocytosis that increases with the peak of constitutional symptoms, with a subsequent fall to baseline.

Patients with tertiary syphilis and JHR may experience only a mild fever; a fever and the above constitutional signs; or a fever, constitutional signs, and neurologic signs that may include confusion, stupor, seizures, and focal neurologic signs. Histologic changes in the skin lesions in patients with secondary syphilis and JHR begin initially with transient acute inflammation 4 to 6 hours after beginning antibiotic treatment. The capillaries and small blood vessels become congested. Later, neutrophils infiltrate the lesion coming from the congested vessels and the lesion becomes edematous. The acute inflammatory process subsides by 18 hours and is gone by 72 hours. There is limited literature describing central nervous system (CNS) pathologic changes from a JHR. Heyman and colleagues reported that the findings were similar to the skin lesions with vascular congestion, acute inflammation, and edema. In another study, one patient with general paresis developed a JHR with a fever and multiple seizures following penicillin treatment. The pathogenesis of JHR remains controversial. The literature has considered endotoxins, complement, histamine, tumor necrosis factor, release of toxic factors in dying...
spirochetes, and cytokines; however, to date, there has been no consensus regarding the cause. Transient significant serum elevations of several cytokines (interleukins [ILs] 6, 8, and 10) during a JHR have been reported, but their levels in cerebrospinal fluid (CSF) levels have not been analyzed.

Here we report a patient with general paresis who, following penicillin therapy, developed an acute JHR with a transient neutrophil pleocytosis and elevated cytokines in his CSF, suggesting that cytokines participate in the CNS aspects of JHR.

Report of a Case

A 55-year-old man worked as a construction worker and was regularly seen at a Veterans Affairs hospital for anxiety and alcoholism since 1999. He was not found to have dementia, hallucinations, paranoia, or complications of alcoholism, and his neurologic examination result was normal. Figure 1 shows his magnetic resonance image in 2009, which was interpreted as normal. In early 2010, a psychologist noted anxiety and pressured speech but no dementia; however, 2 months later, he was hospitalized for delusions and confabulations. Neuropsychological testing results showed moderate cognitive impairment with poor executive functioning. No syphilis testing was performed.

By September 2010, his dementia worsened, he developed his first seizure, and he required a legal guardian. The electroencephalogram showed diffuse slowing and spiking in the left hemisphere, and he was started on treatment with levetiracetam. A serum Treponema pallidum–specific test result returned negative (false negative as a repeat test result 2 months later was positive).

In December, he was admitted to a neurology ward. He was afibrile with dementia, equal reactive pupils, urinary incontinence, fluctuating mental status, hallucinations, dys equilibrium, hyperreflexia, and Babinski signs. Results from CSF tests were abnormal (Table). Cerebrospinal fluid was frozen at −20°C and later sent for cytokine analysis. Figure 1 shows his magnetic resonance image that was interpreted as showing generalized atrophy, no areas of gadolinium enhancement, and a remote small thalamic lacunar infarction. Extensive workup failed to find other causes of the dementia.

The diagnosis of general paresis was made. He was started treatment with intravenous penicillin G. Four hours later, he spiked a fever of 102.6°F; became agitated, obtunded, tachycardic, and hypertensive; experienced several generalized seizures; and had a macular nonpruritic rash over his chest and arms. His CSF test results were abnormal and different from the initial CSF results (Table). He continued to receive intravenous penicillin G for 14 days. His temperature returned to normal in 1 day, the rash cleared over several days, and the seizures stopped. He became alert and cooperative but remained demented.

Follow-up evaluation at 7 months showed he continued to have severe dementia but no seizures. Repeat CSF test results are listed in the Table. Follow-up evaluation at 15 months...
Methods

Cerebrospinal fluid samples were stored at −20°C and shipped from New Mexico to the University of Colorado School of Medicine for analysis on dry ice and later thawed on ice. The CSF sample was diluted and processed per the manufacturer’s instructions for the Quansys Q-Plex array using the Human Cytokine Screen antigen standard 96 well plate to multiplex 16 cytokines per sample per well (IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12/70, IL-13, IL-15, IL-17, IL-23, interferon γ, tumor necrosis factor α, and tumor necrosis factor β). Cytokine arrays were imaged on the Quansys Q-View Imager and cytokine concentrations provided by the Quansys Q-View imaging software. Each sample was run in parallel with a deidentified CSF sample obtained from the University of Colorado Hospital laboratory with a normal CSF profile. Cerebrospinal fluid studies were approved as institutional review board exempt by the Colorado Multiple Institution Review Board.

Both the acute and convalescent CSF samples were obtained as previously described and evaluated in parallel using the BD Biosciences Multi-Analyte ELISAArray kit according to the manufacturer’s instructions for IL-10, IL-8, and IL-1β. Serially diluted samples were run in parallel with positive control samples and a negative CSF sample, and qualitative optical density values were obtained using the VictorX multilabel plate reader (PerkinElmer). Optical density values are expressed as fold increase over negative control values.

Frozen CSF obtained during the JHR was sent to the laboratory of Christina Marra, MD (University of Washington School of Medicine, Seattle), for its *T pallidum* reverse transcription polymerase chain reaction assay.39

Results

Acute and convalescent CSF was obtained from the patient during the JHR and 7 months later, respectively. Initial acute CSF was analyzed using the Quansys Biosciences Q-Plex chemiluminescent reader according to the manufacturer’s instructions. The CSF sample was run neat and at dilutions of 1:10 and 1:100 to ensure appropriate dilution of cytokine concentrations. Concentrations of cytokines in Figure 2 from the acute CSF sample are presented based on data from a 1:10 dilution series. Following removal of presumed false-positive results and background signal based on a control CSF sample from a patient with no CNS disease and a normal CSF profile, the patient had evidence of elevated IL-1β (293 pg/mL), IL-8 (3186 pg/mL), IL-10 (192 pg/mL), and IL-15 (418 pg/mL). When the convalescent CSF sample was obtained, we completed a qualitative enzyme-linked immunosorbent assay (ELISA) for IL-10, IL-8, and IL-1β (Multi-Analyte ELISAArray kit; SABiosciences) on both acute and convalescent CSF samples to ensure that (1) we could repeat our initial CSF data with an independent ELISA test and that (2) convalescent CSF showed resolution of inflammatory cytokines. We found a significant qualitative signal in the acute CSF sample for IL-8, and this signal was absent in the convalescent CSF sample (Figure 2). Fold changes were calculated using the fold change in optical density compared with a negative CSF control sample.

Discussion

Our patient developed a classic JHR beginning 4 hours after the first penicillin dose for his general paresis. He developed a fever, tachycardia, confusion, obtundation, and several generalized seizures, along with a transient neutropenia. The entire episode lasted 18 hours. During that time, a lumbar puncture demonstrated a dramatic change in CSF composition from CSF obtained before administration of penicillin. The CSF white blood cell count jumped from 5/μL to 295/μL (to convert to ×10^9 per liter, multiply by 0.001), with a shift from predominately lymphocytes to predominately neutrophils. While the glucose and protein levels remained unchanged, the CSF demonstrated very elevated levels of IL-8 and likely IL-1β, IL-10, and IL-15. Blood during that period was not available for cytokine analysis.

Prior studies of patients with a JHR have shown evidence of elevated serum levels of IL-6, IL-8 and IL-10.14–18 To our knowledge, this is the first report of elevated CSF cytokine levels in a patient with a JHR.

Our data show that IL-8 is increased to levels of 3186 pg/mL (18-fold increase over control levels) during acute JHR and then resolved on retesting of convalescent CSF. Interleukin 8 is also known as CXCL8, is an α chemokine, and functions in chemotaxis for neutrophils and T lymphocytes.20,21 In the brain, IL-8 is produced by microglia and astrocytes and can bind to the CXCR2 receptors on astrocytes, microglia, and neurons.22,23 Also, glial-produced IL-8 may alter neuronal excitation by modulating Ca^{2+} levels at the presynapse.24 Studies of patients during sepsis and brain injury have shown that IL-8 is associated with increases in blood-brain barrier permeability as well.25,26 Our report supports a temporal association in the CSF of elevated IL-8 and increased acute CNS inflammation secondary to syphilis and JHR.
Elevated CSF Cytokines in JHR

Our initial analysis of acute CSF cytokines during the JHR revealed evidence of increased IL-1β, IL-10, and IL-15, in addition to IL-8. In our repeat qualitative ELISA, we did not detect IL-10 or IL-1β, and IL-15 was not tested. The underlying cause for this discrepancy is not clear and must be interpreted with more caution than our results with IL-8: (1) The repeat qualitative ELISA may not be as sensitive as our initial quantitative cytokine analysis using the Quansys chemiluminescent system. (2) The quantitative increases in IL-1β, IL-10, and IL-15 seen in the Quansys assay but not confirmed by ELISA may have been false-positive results. (3) The additional freeze-thaw cycle for the acute CSF sample may have resulted in degradation of less-abundant small peptides. To better understand the CNS pathogenesis of JHRs, a prospective, controlled study with more patient numbers is needed.

Other spirochetes that infect the CNS alter similar cytokine responses. B. burgdorferi infection in the CNS results in elevated IL-17, CXCL10, and CXCL8 compared with control samples, suggesting that Th1-type and Th17 responses are important in spirochete infections at early points. Recent studies have shown that elevated CXCL13 in the CSF of patients with acute, untreated neurosyphilis and neuroborreliosis is a sensitive and specific biomarker of disease. It is likely that acute inflammatory responses to spirochete infections in the CNS are based on stereotypic immune responses with overlapping pathogenesis. Our data from this patient provide evidence of general inflammatory reactions with IL-8 and support the important role of Th1-type (CXCL10) responses to spirochete infections in the CNS.

Neurosyphilis most commonly presents as a meningeal syndrome, and other acute meningeal infections may cause elevations in CSF cytokines. In cases of herpes simplex and herpes zoster meningitis, interferon γ and IL-6 were significantly elevated in the CSF, suggesting a role of Th1-type responses in meningeal infections. Prospective studies evaluating the presence of specific cytokines in the CSF of patients with neurosyphilis or JHRs in association with clinical data and outcomes are required to understand the prognostic significance or clinical use of complex inflammatory profiles in the CSF of infected patients. To our knowledge, this is the first investigation into the CSF cytokine profile of a patient with JHR and general paresis. Because we did not measure CSF cytokines in the pre-JHR CSF, we cannot be certain the cytokine elevation was part of the JHR and is not present in all patients with neurosyphilis. However, the CSF cytokines were normal in the follow-up sample, and the elevated cytokines were associated with an acute CSF neutrophilia, suggesting the elevated CSF cytokines may have contributed to the neurologic manifestations of the JHR. As further data emerge regarding the innate inflammatory response during episodes of acute infection and inflammation, targeted therapies to modulate this system may improve future outcomes and modify the JHR.

REFERENCES


