Herpes Simplex Encephalitis during Treatment with Tumor Necrosis Factor-α Inhibitors

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Abstract

We report 3 cases of herpes simplex virus encephalitis in patients receiving tumor necrosis factor-alpha (TNF-α) inhibitors for rheumatologic disorders. Although TNF-α inhibitors have been reported to increase the risk of other infectious diseases, to our knowledge, an association between anti–TNF-α drugs and herpes simplex virus encephalitis has not been previously described.

Tumor necrosis factor-alpha (TNF-α) inhibitors are widely used for the treatment of rheumatologic diseases and other inflammatory disorders. These agents—in particular, the monoclonal antibodies infliximab and adalimumab—have been associated with a variety of infections, particularly granulomatous diseases [1–3]. To our knowledge, encephalitis due to herpes simplex virus (HSV) has not been previously described in association with TNF-α inhibitor therapy.

Case reports

Patient 1 was a 44-year-old man who was hospitalized for syncope associated with bradycardia. His medical history included psoriatic arthritis, which had been treated with infliximab for 26 months. On the second day of hospitalization, he developed fever (temperature, ≤ 38.9°C [≤ 102°F]), complained of a headache, and developed altered mental status, which was characterized by flattened affect, slow mental processing, and memory
disturbances. On day 2 of hospitalization, magnetic resonance imaging (MRI) of the brain was performed, and the findings were normal. Routine laboratory studies yielded the following results: hematocrit, 43%; white blood cell (WBC) count, 10,060 cells/mm$^3$ (72% neutrophils, 16% lymphocytes, and 12% monocytes); and platelet count, 239,400 platelets/mm$^3$.

Fever continued on day 3 of hospitalization, and the patients neurologic changes persisted. A lumbar puncture was performed; examination of cerebrospinal fluid (CSF) specimens revealed the following values: WBC count, 50 cells/mm$^3$ (34% neutrophils, 63% lymphocytes, and 2% monocytes); red blood cell (RBC) count, 10 cells/mm$^3$; glucose level, 70 mg/dL; and protein level, 39 mg/dL. Gram staining was negative for organisms. Empirical therapy with vancomycin, ampicillin, cefotaxime, doxycycline, and acyclovir (10 mg/kg intravenously every 8 h) was initiated. Bacterial cultures and CSF polymerase chain reaction (PCR) assays for HSV and enteroviruses were negative. Serologic studies for arboviruses (including West Nile virus), Borrelia burgdorferi, Rickettsia rickettsii, Ehrlichia chaffeensis, and Treponema pallidum yielded negative results.

On day 5 of hospitalization, antimicrobial therapy was narrowed to doxycycline and acyclovir. MRI was repeated, with focal right temporal lobe inflammatory changes and edema noted. An additional lumbar puncture, which was performed on day 6 of hospitalization, revealed a CSF WBC count of 353 cells/mm$^3$ (86% lymphocytes and 14% monocytes), an RBC count of 8 cells/mm$^3$, a CSF glucose level of 54 mg/dL, and a protein level of 58 mg/dL. HSV PCR of the second CSF sample was positive for HSV-1 DNA (HSV-1 load, 1,308,000 copies/mL). Intravenous acyclovir (increased to 15 mg/kg every 8 h) was continued for a 21-day course.

During follow-up, the patient’s mental status normalized, and he returned to work as a heavy equipment operator, although he continued to have subtle neuropsychiatric changes that resolved over the following year. His psoriatic arthritis became symptomatic, but infliximab treatment was not restarted.

Patient 2 was a 47-year-old woman who was hospitalized with a 9-day history of headache associated with fever, vomiting, anorexia, malaise, photophobia, and meningismus. She had rheumatoid arthritis and was being treated with adalimumab and methotrexate. The patient had no recognized history of genital herpes. Evaluation included MRI of the brain with contrast, which revealed right–temporal lobe edema and inflammation. CSF examination demonstrated the following values: WBC count, 100 cells/mm$^3$ (99% lymphocytes); glucose level, 54 mg/dL; and protein level, 134 mg/dL. Routine laboratory studies revealed the following values: hematocrit, 41%; WBC count, 7000 cells/mm$^3$ (50% neutrophils, 35% lymphocytes, and 14% monocytes); and platelet count, 277,000 platelets/mm$^3$. Empirical therapy was initiated with vancomycin, ampicillin, cefotaxime, and acyclovir. Blood, urine, and CSF bacterial cultures all yielded negative results. HSV PCR of CSF specimens was positive for HSV-2. Antibacterial treatment was discontinued, and intravenous acyclovir treatment was continued for 21 days. During short-term follow-up, the patient’s condition had improved, but she was noted to have persistent, subtle neuropsychiatric changes.

Patient 3 was a 56-year-old woman who presented with a 1-day history of frontal headache, fever, and nausea. The patient had symmetrical inflammatory polyarthritis and had received adalimumab for 15 months (in addition to methotrexate and prednisone). She was febrile (temperature, 39.6°C [≥103.2°F]) and had severe photophobia, but the findings of her physical examination were otherwise unremarkable. She was empirically treated with vancomycin, ceftriaxone, and intravenous acyclovir (10 mg/kg every 8 h). MRI of the brain with contrast yielded unremarkable findings. Examination of CSF specimens revealed the
following values: WBC count, 7 cells/mm$^3$; RBC count, 8 cells/mm$^3$; glucose level, 47 mg/dL; and protein level, 41 mg/dL. The results of Gram stain and bacterial culture were negative. HSV PCR of CSF yielded negative results. The fever persisted, and the patient’s mental status deteriorated. On day 6 of hospitalization, MRI was repeated and revealed abnormal signal in the temporal lobes, right greater than left (Figure 1). On day 8 of hospitalization, she underwent an additional lumbar puncture, which demonstrated a WBC count of 483 cells/mm$^3$ (99% lymphocytes), an RBC count of 5 cells/mm$^3$, a normal glucose level, and a protein level of 72 mg/dL. HSV-1 DNA was detected in a CSF specimen by PCR (HSV-1 level, 6600 copies/mL). In response to the patient’s clinical deterioration, her acyclovir dose was increased to 15 mg/kg every 8 h, to complete 21 days of therapy. She defervesced, and her mental status improved, although she continued to have short-term memory difficulties and proximal muscle weakness. She was discharged to an inpatient rehabilitation facility on hospital day 27. Adalimumab therapy was not restarted.

**Discussion**

The TNF-$\alpha$ inhibitors have become standard therapy for a variety of inflammatory conditions, including inflammatory arthritis and bowel disease. These agents offer targeted immunosuppression with fewer long-term adverse effects than traditional immunosuppressive agents, such as corticosteroids. TNF is a cytokine synthesized mainly by macrophages in response to various stimuli, including viral infection. It exerts its biologic effect by binding to 1 of 2 receptors: TNF-R1 (p55) or TNF-R2 (p75). These receptors serve to stimulate the release of inflammatory cytokines, to coordinate leukocyte chemotaxis, and to up-regulate expression of endothelial adhesion molecules and chemokines [4]. TNF-$\alpha$ has an important role in granuloma formation and is a key host cytokine in controlling granulomatous infection with mycobacterial and fungal pathogens [3, 4].

TNF-$\alpha$ inhibition has been associated with an increased risk of infections, notably tuberculosis, other bacterial infections, and fungal infections [1–3]. Infectious complications have been more frequent in patients receiving monoclonal antibody preparations (infliximab and adalimumab) than with the fusion protein etanercept. TNF-$\alpha$ inhibitors are less clearly linked to an increased risk of viral infection, although cutaneous HSV disease has been reported in patients receiving TNF-$\alpha$ inhibitors [5], and there is a growing body of evidence that TNF-$\alpha$ inhibitor therapy is associated with an increased risk of herpes zoster [6]. Animal models suggest that TNF-$\alpha$ is an important element of the innate immune response to HSV-1 encephalitis [7]. These findings suggest that an increase in the risk of severe HSV infection in relation to the use of TNF-$\alpha$ inhibitors is biologically plausible.

We identified 3 adults who developed herpes simplex virus encephalitis (HSE) during treatment with monoclonal antibody TNF-$\alpha$ inhibitors, an association which (to our knowledge) has not previously been reported. All patients ultimately demonstrated characteristic temporal lobe involvement by MRI, had CSF PCRs positive for HSV DNA, and significantly improved after receiving acyclovir therapy. As judged by serologic data, 70% of patients develop HSE as a consequence of HSV reactivation [8]. Unfortunately, acute and convalescent sera were not available from the patients described here to assess primary versus recurrent HSV infection. Although > 95% of HSE cases in adolescents and adults are attributed to HSV-1, occasional cases caused by HSV-2 are well described [9], as was one of the patients in our series. None of the patients described here had a recognized diagnosis of orolabial or genital herpes.

It is noteworthy that 2 patients initially had normal MRIs and negative results of CSF HSV PCR assays. More than 90% of adult patients with HSE will have temporal lobe abnormalities noted by MRI [10] and a positive HSV PCR result at presentation [11].
However, investigators have reported that these diagnostic tests may be negative for 5%–27% of patients with HSE if they are performed very early in the course of the illness [12]. Recently published guidelines on the management of encephalitis emphasize the need to repeat HSV PCR, if the results are initially negative, in 3–7 days, if the clinical course remains suggestive of HSE and no alternative diagnosis has been established [13]. In that situation, repeating the neuroimaging would also be appropriate. Our experience suggests that, at least in patients receiving TNF-α inhibitors with a clinical presentation compatible with HSE, consideration should be given to continuing empirical acyclovir treatment until the result of a second CSF HSV PCR is negative or an alternative diagnosis becomes evident.

Even with appropriate empirical antiviral treatment, mortality from HSE at 1 year is 14%, and 22% of survivors will have residual neurological and cognitive deficits [14]. Two of the patients in the present report demonstrated progressive neurologic and radiologic disease while receiving the standard dosage of acyclovir (30 mg/kg/day). Data from neonates with HSE suggest improved outcomes with higher acyclovir dosages of 45–60 mg/kg/day [15]. On the basis of these limited data, the unproven assumption that higher doses of acyclovir will produce higher drug levels in central nervous system tissue, and the very low toxicity of acyclovir, many clinicians elect to administer dosages of up to 45 mg/kg/day in adult patients with HSE. However, these high doses of acyclovir have not been prospectively studied in adults, and no routine recommendations about their use can be made [13].

HSE is not a disease that has traditionally been associated with immunodeficiency, but recent studies suggest that some pediatric cases of HSE may be linked to defects in interferon pathways [16]. How TNF-α inhibitor therapy affects the pathogenesis and prognosis of HSE in humans has not been studied, and it is not known whether re-institution of TNF-α blockade would result in relapse or recurrence of HSE. None of the patients described here have been re-challenged with TNF-α inhibitor therapy.

HSE is a rare disease in the general population, with an annual incidence of 1–2 cases per 1,000,000 population [14]. Although our cases series lacks denominator data, these cases suggest that patients receiving TNF-α inhibitors may be at increased risk for HSE, and that the disease manifestations may be atypical in this population. Additional clinical studies are needed to document the strength of this association and define the pathogenesis. We encourage clinicians to be aware of the potential for increased risk of HSE among patients treated with TNF-α inhibitors, and to have a higher threshold for discontinuing empirical acyclovir treatment despite the usual criteria of normal MRI findings and negative HSV PCR results. To better define this emerging association, patients receiving TNF-α inhibitors who receive a diagnosis of HSE should be reported to the US Food and Drug Administration through the MedWatch system (http://www.fda.gov/medwatch).

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References


Figure 1.
Magnetic resonance image for patient 3 on day 6 of hospitalization showing abnormal enhancement involving the right insular cortex, temporal lobes (right greater than left), and bilateral inferior frontal lobes.