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Adjunctive Intravenous Immunoglobulin and Glucocorticoid Therapy in Severe Herpes Simplex Encephalitis with Excellent Outcome Begs for Larger Trials Evaluating Immunomodulatory Therapy

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 21-year-old
Final Diagnosis: Encephalitis
Symptoms: Confusion
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Unusual clinical course

Background: Despite the preponderance of evidence of immune-driven pathophysiology of disease in herpes simplex virus-1 (HSV-1) encephalitis, current treatment paradigms do not officially recommend adjunctive immunomodulatory therapy in addition to acyclovir. This may in part explain the poor long-term outcomes in patients with severe HSV encephalitis. This report is of a 21-year-old man presenting with a 4-day history of nausea, headache, and fever and a diagnosis of HSV-1 encephalitis.

Case Report: We describe the case of a young male with clinically and radiographically severe HSV-1 encephalitis diagnosed by PCR of cerebrospinal fluid (CSF), who demonstrated immediate improvement upon treatment with intravenous immunoglobulin (IVIG, 0.5 g/kg daily ×3 days) in addition to acyclovir and dexamethasone therapy. Acyclovir therapy was extended beyond 21 days due to persistently positive HSV-1 CSF PCR. He developed N-methyl-D-aspartate (NMDA) receptor antibodies at 6 weeks, but his long-term outcome far exceeded expectations. While some of his neurological deficits appear to be permanent, he is living a normal life.

Conclusions: Overwhelming evidence demonstrates that brain injury due to HSV encephalitis is driven by immune reactions stimulated by HSV rather than HSV itself. Nevertheless, use of immunomodulatory therapy such as glucocorticoids and IVIG are left to the discretion of individual clinicians rather than being recommended in treatment guidelines, which instead recommend acyclovir therapy. The present case highlights the potential role of immunomodulatory therapy with IVIG in HSV encephalitis and the importance of early diagnosis and treatment.

Keywords: Encephalitis, Herpes Simplex • Immunoglobulins, Intravenous • Glucocorticoids • Immunomodulation • Neuroimmunomodulation

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Backgraound

Herpes simplex virus-1 (HSV-1) encephalitis is the most common fatal encephalitis, and can occur in immunocompromised and immunocompetent patients [1]. It has an incidence of 2-4 cases/million in the US and worldwide. There is a bimodal distribution, with one peak incidence at < 3 years of age and another in adults aged >50 years, but the majority of cases occur in those over 50, with both sexes equally affected [2-5]. Despite appropriate antiviral therapy, mortality is as high as 25% [2]. Currently, early initiation of acyclovir is the most modifiable aspect of care that influences outcome, but, despite early therapy, nearly two-thirds of survivors will have significant long-term neurological deficits [3-5]. A significant number of patients with HSV-1 encephalitis subsequently develop anti-N-methyl-d-aspartate (NMDA) receptor antibodies [6].

While treatment guidelines recommend directly addressing HSV-1 with acyclovir antiviral therapy, there are no official recommendations on the use of anti-inflammatory agents for this disease [4,5]. A recent review recommended that, for HSV-1 encephalitis, administration of adjunctive immunomodulatory drugs should be initiated during the rise of the inflammatory response, but duration should be limited to reduce undesired effects [7]. These authors also advocate the use of biomarkers of inflammation to identify the optimal treatment duration [7]. We present this case, not only to inspire clinical trials, but also to allow clinicians to weigh the use of glucocorticoid therapy and/or intravenous immunoglobulin (IVIG) in severe HSV-1 encephalitis alongside acyclovir therapy. The present report is of a 21-year-old man with a diagnosis of HSV encephalitis and NMDA-receptor antibodies who responded to early immunomodulatory treatment with IVIG combined with acyclovir and dexamethasone.

Case Report

A 21-year-old man in good health developed headache, fever, and vomiting 4 days before being admitted to our hospital. He presented to an outside hospital 2 days after symptom onset with mental status deterioration and fever. He had negative computerized tomography (CT) scans of the brain and cerebrospinal fluid (CSF) with mild lymphocytic pleocytosis. He was started on intravenous (IV) ceftriaxone and IV acyclovir and was transferred to our hospital by air medevac. On arrival, he showed movement in all his extremities, was breathing spontaneously, and withdrew to painful stimuli, but demonstrated no purposeful movements and did not follow commands. A brain magnetic resonance imaging (MRI) scan showed bilateral, primarily cortically based, asymmetric edema with underlying restricted diffusion involving the frontal lobes, insula, and temporal lobes, with the right side greater than the left, and with relative sparing of the basal ganglia (**Figure 1**). These

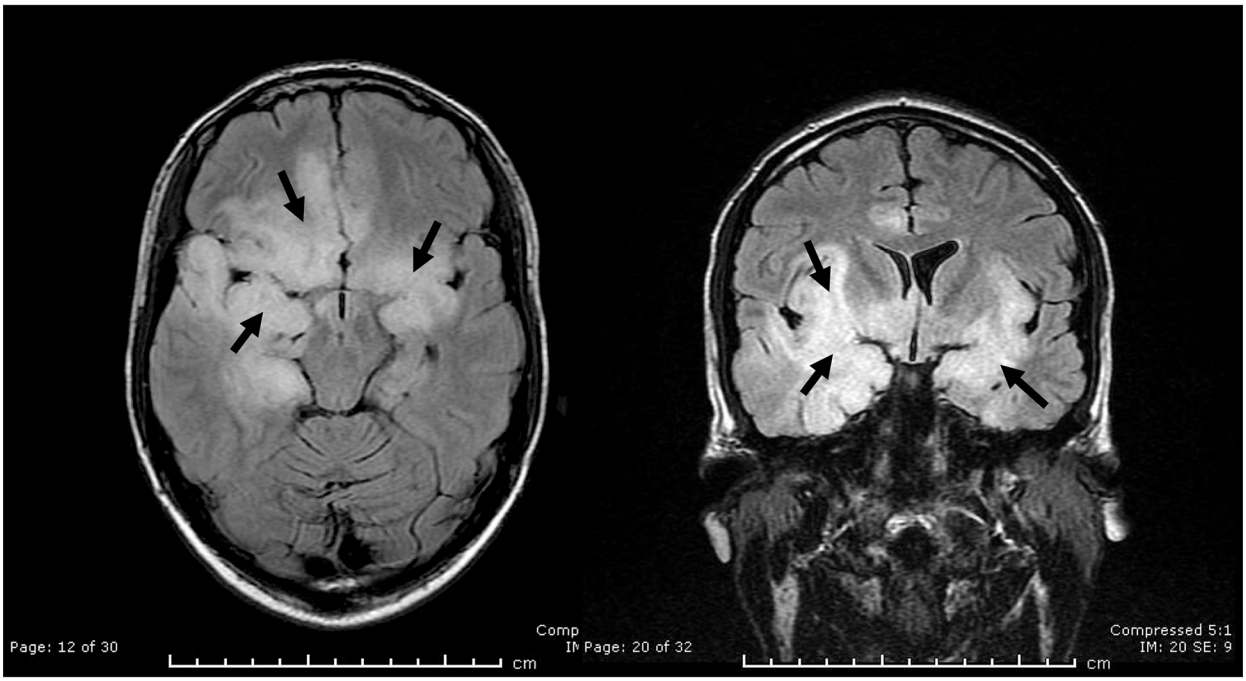

Figure 1. Brain MRI of a 21-year-old man with severe HSV-1 encephalitis showing bilateral, primarily cortically based, asymmetric edema with underlying restricted diffusion involving the frontal lobes, insula, and temporal lobes, right greater than left, with relative sparing of the basal ganglia. Arrows point to some areas of involvement. MRI, magnetic resonance imaging; HSV-1, herpes simplex virus 1.

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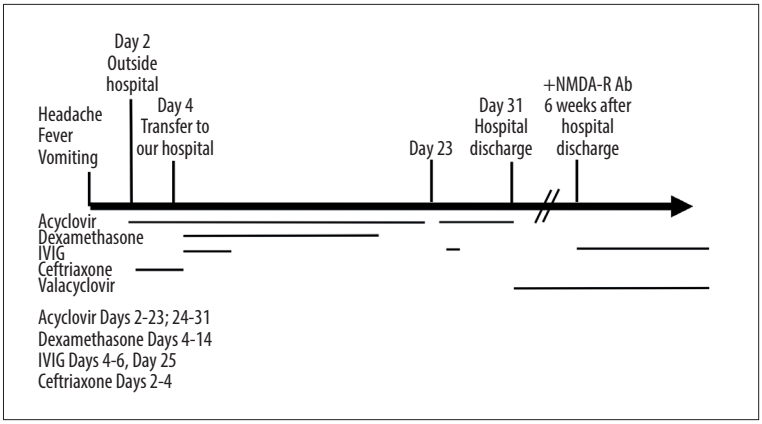

Figure 2. Case report timeline highlighting: i) early initiation of IVIG and methylprednisolone; ii) continuation of acyclovir beyond the usual 21 days due to persistently positive HSV-1 PCR in CSF; iii) the development of NMDA-receptor antibodies requiring more immunomodulation at 6 weeks. IVIG – intravenous immunoglobulin G; HSV-1 – herpes simplex virus 1; PCR – polymerase chain reaction; CSF, cerebrospinal fluid; NMDA – N-methyl-D-aspartate.

findings were deemed highly suspicious for a viral encephalopathy to include herpes encephalitis. The right-sided brain edema resulted in a mild mass effect upon the right lateral ventricle without hydrocephalus or significant midline shift. The underlying restricted diffusion was deemed atypical and suggested advanced disease with underlying cytotoxic edema/infarction. The bilateral paramedian frontal lobe distribution of disease raised suspicion for possible superimposed anterior cerebral artery territory infarction. Mild associated ill-defined leptomeningeal enhancement in the right middle cranial fossa and right sylvian region was also noted. CSF analysis showed a white blood cell (WBC) count of 21 cells/mm^3 (59% lymphocytes and 41% monocytes), red blood cell (RBC) count of 3 cells/mm^3, glucose 75 mg/dL, and total protein 41 mg/dL. CSF polymerase chain reaction (PCR) for HSV-1 was positive (21 cycle). Acyclovir 10 mg/kg q8hr and dexamethasone 10 mg q12hr were continued. IVIG (Privigen; CSL Behring, King of Prussia, PA, USA) was initiated at 0.5 g/kg/day for 3 days starting on the day of admission. Within 48 hours, the patient was awake and making conversation in full sentences with his family, although he did not recognize them and he had complete retrograde amnesia to all events prior to illness, including his childhood, his parents, and other family members. A repeat MRI 1 week into the hospital stay showed no significant change. Dexamethasone slow weaning was initiated.

A repeat CSF analysis after 3 weeks of acyclovir therapy showed a WBC count of 55 cells/mm^3 (77% lymphocytes and 22% monocytes) and an RBC count of 5 cells/mm^3, glucose of 65 mg/dL, and total protein of 54 mg/dL. After being stopped for 1 day, the acyclovir was given for an additional week based on HSV-1 PCR of CSF being persistently positive, although near the upper cycle threshold limit of 40. An MRI at 4 weeks showed decreased abnormal cortical thickening and increased T2 signal involving the frontal and temporal cortex, and persistent patchy enhancement. The previously noted restricted diffusion suggesting edema or infarction had resolved. Another dose of IVIG 0.5 g/kg was given at 4 weeks. The patient was discharged on valacyclovir 1 g p.o. q8hr. A CSF analysis 6 weeks after hospital discharge revealed NMDA-receptor antibodies and additional courses of IVIG treatment were restarted. He had chronic symptoms of Kluver-Bucy syndrome. Four years after his hospital discharge he completed his undergraduate studies and 5 years later he is alive and doing reasonably well. A summary timeline in presented in **Figure 2**.

Discussion

This case demonstrated that immunomodulation with IVIG and glucocorticoid therapy alongside acyclovir resulted in marked improvement in a severe case of HSV-1 encephalitis, and that this approach requires further study. Despite high illness severity, demonstrated by his depressed level of consciousness, his brain MRI (**Figure 1**), and complete amnesia, this patient made a remarkable recovery. This is probably related to his young age as well as the potent immunomodulatory therapy that he received very early in the illness course before brain injury became permanent. Brain injury from HSV-1 encephalitis is believed to be largely immune-mediated, given that i) immunocompromised patients do not have increased rates of HSV-1 encephalitis despite muco-cutaneous disease being commonplace; ii) brain biopsies from immunocompromised patients with HSV-1 encephalitis show relatively mild inflammation [3]; iii) HSV-infected cells are targets of local cytotoxic T-cells [8]; iv) levels of cytokines and nitric oxide [9], not CSF viral load [10], correlate with levels of brain injury, and immune cell infiltration correlates with degree of demyelination [8]; v) HSV-1 IgM immune complexes have been seen in the cerebral vasculature in a patient with HSV-1 encephalitis [11]; vi) interleukin-4 administration can increase disease severity in an HSV-1 encephalitis mouse model [12]; vii) NMDA-receptor antibodies have been detected in the serum and/or CSF of 30% of patients retrospectively after HSV-1 encephalitis [7].

Despite this preponderance of evidence on the immunopathology in HSV-1 encephalitis, there are no formal recommendations on the use of immunomodulators in treating HSV-1 encephalitis

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to supplement antiviral therapy. A recent extensive review demonstrates an overwhelmingly favorable effect of glucocorticoids when added to acyclovir, although it is important to understand that the vast majority of patients so treated were younger; presumably, in these patients, a robust immune response to the virus would require mitigation [13]. The potential benefit of IVIG in HSV encephalitis was shown 35 years ago, yet despite the fact that HSV encephalitis is the most common fatal sporadic encephalitis in the US, supportive clinical trials have yet to be conducted [14]. More recently, 2 other studies using a murine HSV encephalitis model demonstrated a survival benefit of IVIG compared with untreated mice, with reduced monocyte infiltration [15,16]. Ramakrishna et al demonstrated that the combination of IVIG plus acyclovir significantly reduced brainstem inflammation in the murine model of HSV encephalitis from days 7 to 21 post-infection. Even more interesting was the finding that HSV-1-specific CD8+ T-lymphocytes were increased by IVIG therapy, suggesting that in addition to providing an immunomodulatory effect, IVIG appeared to result in localized increased antiviral immunity. Finally, IVIG reduced production of the pro-inflammatory chemokines CXCL1/GRO-alpha and interleukin-6, and increased CCL5/Rantes, results that could be anticipated, with the influx of CD8+ T-lymphocytes with HSV activity [17].

The same group subsequently showed that antiviral therapy is not sufficient to protect against fatal HSV encephalitis but that triggering an anti-inflammatory mechanism is critical to improving outcomes. They showed that IVIG induces regulatory CD4+ T-lymphocytes that provide an IL-10-mediated anti-inflammatory effect in the brainstem of HSV-infected mice [18].

In our patient, the effect upon the addition of IVIG was immediate and undeniable. Within the first 2 doses of IVIG, when dexamethasone was already being administered, a notable improvement in responsiveness and interactive behavior was noted. Obviously, it is impossible to know what the outcome would have been in this case with standard acyclovir therapy alone, or with added dexamethasone without IVIG. However, the timing of improvement coinciding with IVIG initiation, a best-case scenario outcome in such a severe case, and strong animal data advocating the benefits of IVIG together indicate the low probability of such an outcome without the IVIG. What is unclear in the pathophysiology underlying the morbidity of the persistent neurological deficits after viral encephalitis is the role of virally driven neuronal injury vs the development of autoantibodies. A significant percentage of patients with HSV encephalitis develop NMDA-receptor antibodies. In this particular patient, the receipt of IVIG and glucocorticoid therapy early in the course of illness was insufficient to halt the development of NMDA-receptor antibodies. Whether continuing IVIG continuously after hospital discharge would have halted the development of NMDA-receptor antibodies is unknown. Only clinical studies can evaluate whether receipt of acyclovir plus immunomodulatory therapy reduces autoantibody production compared with acyclovir alone.

Conclusions

Based on strong scientific data, we utilized dexamethasone and high-dose IVIG therapy in addition to standard acyclovir, and achieved a 'best-case scenario' result in what initially appeared would be a catastrophic case of HSV-1 encephalitis. The clinical and functional outcome of the patient far exceeded expectations based on illness severity at the time of presentation.

We strongly suggest that this case serves as an inspiration for a larger clinical study evaluating IVIG with or without concomitant glucocorticoids in HSV-1 encephalitis, or perhaps viral encephalitis in general. While studies have looked at glucocorticoids as treatments, IVIG studies are lacking. Currently there are 2 trials listed on clinicaltrials.gov evaluating HSV encephalitis, including steroid and NMDA-receptor antibodies, but their status is listed as 'unknown.' It is unfortunate that funding of clinical trials studying diseases such as HSV and other forms of viral encephalitis receive lower funding priority due to their low prevalence, despite poor outcomes overall. This case has highlighted the potential role of immunomodulatory therapy with IVIG in HSV encephalitis and the importance of early diagnosis and management.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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