ABSTRACT
Introduction: Herpes simplex virus (HSV) has been speculated to play a role in migraine headache pathophysiology. We present the first successful migraine headache treatment with therapy specifically targeting HSV infection.

Case Presentation: A previously healthy 21-year-old white female college student woke up one morning with a visual aura consisting of scintillating scotoma followed by headache onset. At presentation she described the headache as severe and throbbing in nature with accompanying nausea and mild confusion. The scotoma resolved in 1 hour; however, the headache persisted for the next 24 hours. Nausea and cognitive dysfunction lasted for 3 and 9 days, respectively. The patient started taking nonsteroidal anti-inflammatory drugs during this time. Approximately 2 days after resolution of the initial presentation, her symptoms recurred.

Discussion: Famciclovir and celecoxib may work synergistically against HSV. The virus may play a role in the pathophysiology of migraine headaches, and this is the first case report of successful migraine headache treatment with these medications. Further studies are needed to elucidate the efficacy of these medications in treating migraine disorder.

INTRODUCTION
Migraine headache pathophysiology has not been fully elucidated. Previous studies point to multifactorial genetic, chemical, and anatomic origins. Researchers have observed that migraine tends to run in families and is considered to be at least partially heritable in nature. Others describe the actual physical phenomena observed among patients with migraine as consisting of trigeminovascular system activation, cortical spreading depression, and neuronal sensitization. It appears that a triggering event in a genetically predisposed patient can initiate a cascade resulting in the headache experience. Specifically, trigeminal ganglion activation seems to be a common early observation among patients with migraine. Herpes simplex virus (HSV) has been known to reside within the trigeminal ganglion and is speculated to play a role in migraine headache pathophysiology. Treatments to target HSV infection may be important in migraine headache management.

CASE PRESENTATION
Presenting Concerns
A previously healthy 21-year-old white female college student woke up one morning with a visual aura consisting of scintillating scotoma followed by headache onset. At presentation she described the headache as severe and throbbing in nature with accompanying nausea and mild confusion. The scotoma resolved in 1 hour; however, the headache persisted for the next 24 hours. Nausea and cognitive dysfunction lasted for 3 and 9 days, respectively. The patient started taking nonsteroidal anti-inflammatory drugs during this time. Approximately 2 days after resolution of the initial presentation, her symptoms recurred.

A neurologist was consulted, and the diagnosis of acute migraine headache was made. A magnetic resonance imaging scan of the patient’s brain revealed several nonspecific hyperintensities in the pericortical frontal lobe. The patient had no history of cold sores. HSV serology was not performed.

Therapeutic Interventions and Treatment
During the next three months, the patient began a trial of several migraine headache treatments including triptans, beta blockers, prednisone, and injections of botulinum toxin. Most of the treatments provided only mild symptomatic improvement. Her difficulty with higher cognitive functions, especially concentration, persisted. She started to experience difficulty with her college coursework and had to take an excused absence for the semester. Concurrently, her sleep quality deteriorated significantly.

Follow-up and Outcomes
Seven months after her initial presentation, our patient began to take famciclovir and celecoxib, as prescribed by her treating physician. She reported substantial relief of her symptoms within 5 days and an immediate improvement in sleep quality. Her mental clarity returned with subjective improvement of headache symptoms, and she was able to return to her full college course load while taking maintenance doses of famciclovir and celecoxib. At 3 years after onset of symptoms, and 15 months after starting famciclovir and celecoxib therapy, our patient has experienced significant improvement of headache symptoms, beta blockers, prednisone, and injections of botulinum toxin. Most of the treatments provided only mild symptomatic improvement. Her difficulty with higher cognitive functions, especially concentration, persisted. She started to experience difficulty with her college coursework and had to take an excused absence for the semester. Concurrently, her sleep quality deteriorated significantly.
Table 1. Case timeline

<table>
<thead>
<tr>
<th>Date</th>
<th>Events and intervention</th>
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<tbody>
<tr>
<td>October 2014</td>
<td>First migraine</td>
</tr>
<tr>
<td>November 2014-August 2015</td>
<td>4 migraines, each with severe symptoms lasting 5-6 d</td>
</tr>
<tr>
<td>November 2015</td>
<td>10 d/mo severe symptoms</td>
</tr>
<tr>
<td>December 2015</td>
<td>25 d/mo severe symptoms</td>
</tr>
<tr>
<td>January 2016-April 2016</td>
<td>Standard treatment initiated: triptans, beta blockers, prednisone, botox injections</td>
</tr>
<tr>
<td>May 2016</td>
<td>Famiclovir and celecoxib initiated</td>
</tr>
<tr>
<td>May 2016-June 2017</td>
<td>&lt; 2 d/mo mild symptoms</td>
</tr>
<tr>
<td>June 2017</td>
<td>Famiclovir and celecoxib discontinued</td>
</tr>
<tr>
<td>June 2017-September 2017</td>
<td>&lt; 2 d/mo mild symptoms</td>
</tr>
</tbody>
</table>

marked reduction in severity and frequency of migraine symptoms, allowing her to complete her undergraduate coursework and to work fulltime without interruption. After 12 months of treatment, she discontinued scheduled famciclovir and celecoxib therapy, and as of this writing has not reported any increase in severity or frequency of symptoms. A timeline of her case is presented in Table 1.

DISCUSSION

Migraine, which affects approximately 15% of the general population in the US, is a severe headache disorder associated with physical, psychological, and financial morbidity. Migraine accounts for an average of 8.3 days of absenteeism and 11.2 days of productivity per affected individual each year, with an overall estimated cost to employers of $3309 per affected employee. Currently available treatment modalities consist of acute abortive pharmacotherapies, prophylactic pharmacotherapies, and adjunctive therapies. Acute abortive pharmacotherapies include nonsteroidal anti-inflammatory medications, acetaminophen, glucocorticoids, opioids, triptans, and ergots. Prophylactic pharmacotherapies consist of beta blockers, calcium channel blockers, tricyclic antidepressants, selective norepinephrine reuptake inhibitors, and antiepileptic medications. Adjunctive therapies such as acupuncture, biofeedback, massage therapies, and onabotulinumtoxin-A injections also have been described.

There has been much speculation about the relationship between migraine headaches and HSV, which already has been implicated in some forms of cranial nerve (CN) disorders. In 1991, Adour demonstrated that patients with acute herpes labialis also exhibited CN deficiencies involving CNs V, VII, IX, and X. This phenomenon was termed HSV-related polygani- gionitis. In 2003, Thiel et al examined the presence of HSV in postmortem ganglia. By using a specific immunostaining technique, the investigators revealed that HSV-1 and HSV-3 latently resided in the CN V (trigeminal) ganglia. It was then speculated that chronic infection and inflammation of the ganglia by HSV were present in many patients. In 2013, VanElzakker hypothesized that pathologically activated glial cells in the vagal sensory ganglia could cause an exaggerated sickness response that is found in chronic fatigue syndrome. If VanElzakker’s hypothesis is true, then we must ask whether glial cells in the intracranial trigeminal ganglia, pathologically activated by HSV, could initiate migraine.

HSV infection commonly is treated with a ganglioside analog medication. Famiclovir is an example of this class of medication. Cyclooxygenase-2 inhibitors such as celecoxib also have been used to treat HSV infection. In 2005, Gebhardt et al successfully demonstrated that celecoxib inhibited the heat-stressed herpes virus reactivation in mice. Synergy between famciclovir and celecoxib in treating HSV infection has been proposed and studied. A phase 2A randomized study of chronic fatigue syndrome revealed a twofold to threefold symptom improvement in patients treated with famciclovir (Famvir, Novartis International AG, Basel, Switzerland) and celecoxib when compared with placebo.

CONCLUSION

In this case, a substantial improvement in migraine headache symptoms was achieved with the use of famciclovir and celecoxib (both medications with direct antiviral activity toward HSV). This combination of medications was used with definite effect initially as an abortive therapy and subsequently as a prophylactic therapy. On the basis of the current understanding of the pathophysiology of migraine headaches, specifically the role of HSV-mediated trigeminal inflammation in migraine symptomatology and the antiviral characteristics of famciclovir and celecoxib, we believe these medications may work synergistically to treat migraine disorder. We also hypothesize that migraine may be attributable to a reactivation of a latent HSV residing within the trigeminal ganglion. Further prospective trials using famciclovir and celecoxib must be performed in isolation and in combination to elucidate the respective role each may play in treating migraine disorder.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References