

## CHAPTER 37

# TWO HEADACHE PATIENTS WITH THE SAME INFECTION

JEROME GOLDSTEIN, MD

RAGUI H. MICHAEL, MD

## Case 1 History

The first case is that of a 50-year-old male who was diagnosed as having human immunodeficiency virus (HIV) infection in 1985 when HIV testing became available. He believes that he was infected as early as 1977. His headache history started in 1979 with a unilateral headache, primarily on the right side, that occurred about twice a week. He was prescribed propranolol, and the headaches completely disappeared within 6 months. In 1985, his headaches returned. He was re-evaluated at that time, and no obvious reason for the recurrence of his headaches was found. A magnetic resonance imaging (MRI) scan did not reveal the cause of the headaches. Since 1985, the headaches have been intermittent and without a definite pattern. A cytomegalovirus (CMV) infection was discovered in 1994 but there was no change in the headache pattern.

In November of 1997 he complained of motor incoordination manifested by his inability to use a typewriter, lethargy, and some confusion. He characterized the symptoms as “My motor control was turned off.” A repeat MRI revealed an increase in brain atrophy. Extensive psychometric testing was done that did not confirm a new-onset dementia. With a change in anti-retroviral medication, the neurologic symptoms did improve but there was a perceptible increase in the frequency of headache. He noticed that didanosine precipitated his headaches. The headaches became more left sided and the use of Fioricet with codeine and opioids increased. In an effort to treat the headaches more effectively, the patient was prescribed meprobamate, 400 mg, three times a day, and there was a significant reduction in the codeine and opioid use. He also stopped taking

didanosine. His headache episodes decreased significantly since then.

## Questions about Case 1

- Are all HIV-related headaches due to secondary infection or could they be due to the HIV infection itself?
- Can recurrent headaches in patients with HIV be controlled effectively with analgesic medications?
- Is there an association between HIV-associated headache and the medications used to treat HIV?
- Does dementia play a role in the onset of headache in patients with HIV?

## Case 2 History

The second case is that of a 38-year-old male who was diagnosed with HIV infection in 1984, when he was 24 years old. His past medical history is significant for multiple head injuries, throughout his life, resulting in chronic headaches. His first head injury occurred at age 7 years when he was hit by a piece of concrete. Later, he suffered seven more head injuries, all from motor vehicle accidents. Other symptoms include tinnitus at the age of 19, and right-sided Bell's palsy for 6 months followed by left-sided palsy with a residual effect on the left side at the age of 21. The patient was noted also to have scintillations that were greater on the left side.

In 1994, his chronic headache changed. He noted that his headaches were increasing in frequency and duration; they usually started in the afternoon and were triggered by stress. The headache was located over the bifrontal, temporal, and occipital regions of the head. The pain was throbbing and stabbing in nature. The

patient also noted that photophobia and phonophobia accompanied the headache. When seen at our office, he was using an ASA and oxycodone preparation and a combination of ASA, butalbital, and caffeine with codeine to treat his headache without any success. He was also on atenolol, 50 mg every night at bedtime and was also using sertraline and clonazepam for depression. The patient was advised to increase his dose of atenolol to 100 mg every night at bedtime, and amitriptyline was added in a dosage of 25 to 50 mg daily, which resulted in significant improvement in the headache problem.

Recently, he was assaulted while walking on the street. The assault resulted in a right frontal head laceration and daily headache. The computed tomography (CT) scan done to rule out a subdural hematoma was normal.

### Questions about Case 2

- Can HIV infection affect the pattern of a pre-existing headache?
- Is there any interaction between the medications used to treat HIV infection and those used to treat headache?
- What is the role of head trauma in the evolution of HIV-associated headache?
- What is the relationship between Bell's palsy, HIV infection, and HIV-associated headache?

### Case Discussion

Neurologists will be evaluating a large number of the currently asymptomatic HIV-1 infected patients with a new complaint of headache. In the past, HIV-associated headache was thought to be mainly secondary or organic. As the disease continues to change in its evolution and pattern, more primary HIV-associated headaches are being reported. The first case is a clear-cut example of this type of headache. It is also evident that the medication regimen of this patient played a significant role in the headache condition. Later in the evolution of his illness, there was also concern that dementia and/or cerebral atrophy might be contributing to the headache problem by virtue of a secondary process. This was not found to be the case. The introduction of an anxiolytic agent, meprobamate, resulted in significant reduction in the use of opioids and other analgesics.

The second case is that of a pre-existing muscle-contraction and migraine headache condition which changed significantly over the course of the HIV infection. Modifications in the therapy for both the muscle-contraction-type headache and the migraine-type headache resulted in improvement in both conditions.

Neither of the cases reported here revealed any type of opportunistic infection or tumor, confirming more

**TABLE 37-1: HIV-1-Infection-Associated Neurologic Disorders**

Etiology	Disorder
Infection	Aseptic meningitis
	Cryptococcal meningitis
	Cerebral toxoplasmosis
	Progressive multifocal leukoencephalopathy
	Cytomegalovirus encephalitis
	Cytomegalovirus polyradiculopathy
Neoplasm	Cytomegalovirus mononeuritis multiplex
	Primary central nervous system lymphoma
	Metastatic lymphoma
Systemic	Hypoxic encephalopathy
	Sepsis
	Stroke
Functional	Anxiety disorder
	Psychotic depression
Primary aids	AIDS dementia complex
	Distal sensory polyneuropathy
Autoimmune	Guillain-Barré syndrome
	Chronic inflammatory demyelinating polyneuropathy

recent reports of a changing distribution of the headache associated with HIV infection.

### Overview of Headache Associated with HIV Infection

An estimated 1 to 2 million people in the United States are currently infected with HIV-1. In 1995, HIV-1 infection was still the leading cause of death in males aged from 25 to 44 despite the substantial decrease in death rate among people with acquired immunodeficiency syndrome (AIDS).

HIV-1 is a neurotropic virus that can readily invade the central nervous system causing a variety of neurologic disorders. These disorders (Table 37-1) may present as an early finding of the disease or more commonly as a late finding. They are associated with a wide spectrum of symptoms.

One of the most common of these symptoms is headache. Goldstein was the first to report on the importance of HIV-associated headache in the early 1990s. The exact prevalence rate of headache in HIV-1 infection is still unknown. However, there is a predictable increase in the prevalence of headache in the HIV-infected population versus the general population. Recent studies indicate that about 50% of all patients with HIV infection will present with headache at some time during the course of the disease.

HIV-related headaches can be due to HIV-1 infection itself or more commonly to the HIV-associated neurologic

disorders. Increased rates of anxiety and depression also act as comorbid factors that increase the prevalence of headache in HIV-infected patients. In addition, the higher prevalence of substance abuse in the HIV-infected population can result in headache associated with the substances or their withdrawal. Late in the disease, medications used to treat HIV infection or its complications can cause headache. Diagnostic procedures may also increase the prevalence of headache in the HIV-infected population.

During HIV-1 infection, pre-existing migraine headache tends to decrease in frequency. Evers et al. reported in 1998 that HIV infection causes a reduction in the migraine-specific neurogenic inflammation of the cerebral vessels. In contrast, pre-existing tension-type headache tends to increase in frequency, partially due to a significant incidence of aseptic meningitis.

#### Primary HIV-Associated Headache

In recent years, a primary type of headache that is associated with HIV-1 infection is being recognized as a distinct clinical entity. Brew and Miller reported in a retrospective study that acute aseptic meningitis was associated with primary HIV-1 infection. It has been estimated to occur in about 2% of all HIV-1 infections. Acute aseptic meningitis can occur as early as at seroconversion and is usually self-limited but can recur later at any time during the disease. Other causes of primary headache in HIV-1 infection include late-stage HIV-related headache without pleocytosis and chronic headache with a persistent pleocytosis. This kind of headache is usually generalized or unilateral and is not accompanied by nausea, thus resembling tension-type headache.

Primary HIV-associated headache is thought to occur through several mechanisms. One possible mechanism is the alteration of the central pain mechanisms at the level of neurotransmission. This mechanism has been suggested along with the discovery of a definite alteration in serotonin and tryptophan metabolism in HIV infection. Another mechanism proposed is the neurotoxic effect of substances released by HIV-infected macrophages. This mechanism was postulated originally to explain the dementia and neuropathy associated with HIV infection. The precise mechanism of primary HIV-associated headaches, however, remains obscure.

Analgesics can be used to treat the primary headache of HIV infection. Antidepressants in moderate doses are also effective in treating primary HIV-associated headache. It is known that certain analgesics interact with drugs used to treat HIV infection. Acetaminophen and indomethacin decrease the blood levels of zidovudine. On the other hand, valproic acid increases zidovudine blood levels.

#### Secondary HIV-Related Headache

This kind of headache tends to occur later in the disease. Opportunistic infections and tumors are the most likely causes. The most important opportunistic infections are cryptococcal meningitis and toxoplasmosis. The most important tumor associated with HIV infection is primary central nervous system lymphoma. HIV-related headache secondary to opportunistic infection is usually constant and gradual in onset. It is also associated with fever, nausea, and vomiting. HIV-related headache secondary to a space-occupying lesion is usually variable in onset and associated with focal neurologic deficits.

Headache can also be secondary to systemic illness. Patients with *Pneumocystis carinii* pneumonia (PCP) may complain of headache initially before other symptoms such as dyspnea or cough occur. Syphilitic meningitis can present at any time during the course of HIV infection and may be associated with headache. Increased sinusitis is common with HIV infection and is another cause of secondary headache, occurring in 33 to 50% of patients.

Medications used in the treatment of HIV-1 infection or its complications can cause headache. Headache is one of the side effects of antiretroviral medications used to treat HIV-1 infection. Zidovudine was shown to induce headache in up to 50% of patients using the medication. This can result in decreased compliance. The high prevalence of painful conditions associated with the HIV-infected population, including peripheral neuropathy, predisposes that group to analgesic abuse, which, when present and untreated, can induce headache.

New-onset headache in the late stages of HIV infection should always raise the possibility of an opportunistic infection or tumor. An MRI and a CT scan should be done for HIV-associated headache occurring late in the disease. A lumbar puncture is also indicated for cerebrospinal fluid analysis and measuring pressure. The incidence of lumbar puncture headache is lower in HIV-infected patients due to the pathophysiologic changes in the brain caused by the HIV infection.

#### Selected Readings

- Brew BJ, Miller J. Human immunodeficiency virus-related headache. *Neurology* 1993;43:1098–100.
- Centers for Disease Control. Update: mortality attributable to HIV infection among persons aged 25–44 years—United States, 1991 and 1992. *MMWR Morb Mortal Wkly Rep* 1993;42:869–72.
- Centers for Disease Control. Update: trends in AIDS incidence, deaths, and prevalence—United States, 1996. *MMWR Morb Mortal Wkly Rep* 1997;46:165–73.

- Epstein LG, Gendelman HE. Human immunodeficiency virus type 1 infection of the nervous system: pathogenetic mechanisms. *Ann Neurol* 1993;33:429–36.
- Evers S, Brilla R, Husstedt I. Headache and human immunodeficiency virus infection—a systemic review. *Headache Q* 1998;9:129–33.
- Fuchs D, Möller AA, Reibnegger G, et al. Decreased serum tryptophan in patients with HIV-1 infection correlates with increased serum neopterin and with neurologic/psychiatric symptoms. *J Acquir Immune Defic Syndr* 1990;3:873–6.
- Goldstein J. Headache and acquired immunodeficiency syndrome. *Neurol Clin* 1990;8:947–60.
- Holloway RG, Kiebertz KD. Headache and the human immunodeficiency virus type 1 infection. *Headache* 1995;35:245–55.
- Katz DA, Berger JR, Duncan RC. Neurosyphilis. A comparative study of the effects of infection with human immunodeficiency virus. *Arch Neurol* 1993;50:243–9.
- Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS). *J Neurosurg* 1985;62:457–95.
- Lipton RB, Feraru ER, Weiss G, et al. Headache in HIV-1-related disorders. *Headache* 1991;31:518–22.
- Markowitz JC, Rabkin JG, Perry SW. Treating depression in HIV-positive patients. *AIDS* 1994;8:403–12.
- McArthur JC. Neurological diseases associated with human immunodeficiency virus type 1 infection. In: Johnson RT, Griffin JW, editors. *Current therapy in neurological disease*. 4th ed. St. Louis (MO): Mosby-Year Book, Inc.; 1993. p. 146–52.
- O'Neil WM, Sherrard JS. Pain in human immunodeficiency virus disease: a review. *Pain* 1993;54:3–14.
- Price RW. Management of the neurologic complications of HIV-1 infection and AIDS. In: Sande MA, Volbberding PA, editors. *The medical management of AIDS*. 5th ed. Philadelphia: WB Saunders; 1997. p. 197–216.
- Richmond DD, Fischl MA, Greico MH, et al. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. *N Engl J Med* 1987;317:192–7.
- Sanford JP, Sande MA, Gilbert DN, Gerberding JL. *Guide to HIV/AIDS therapy*. Dallas (TX): Antimicrobial Therapy, Inc.; 1993. p. 95–9.
- Singer ES, Kim J, Fahy-Chandon B, et al. Headache in ambulatory HIV-1-infected men enrolled in a longitudinal study. *Neurology* 1996;46:487–94.
- Small CB, Kaufman A, Armenaka M, Rosenstreich DL. Sinusitis and atopy in human immunodeficiency virus infection. *J Infect Dis* 1993;167:283–90.

### Editorial Comments

*The challenge to neurologists in evaluating patients with HIV infection is to diagnose and exclude serious secondary causes of headache and to help with their management. Exacerbation of common primary headache disorders is emphasized in Dr. Goldstein's second case. However, the first case represents an increasingly more common headache seen in HIV patients, that of primary HIV-associated headache. This entity requires special attention and must be differentiated from all other types of headache in HIV patients. Once recognized, it usually can be managed successfully, as in the case presented.*