

Letter to the Editor

Common variable immunodeficiency presenting as herpes simplex virus encephalitis

To the Editor:

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders, with the common end point being decreased production of functional antibodies leading to recurrent and often severe bacterial infections. Here we present 3 cases of CVID with protracted histories of multiple bacterial infections, but the diagnosis of CVID was made only after episodes of herpes simplex virus (HSV) encephalitis (HSVE). These are the first described cases of CVID presenting with HSVE.

Patient 1. Patient 1 was a 54-year-old woman with a past history of pneumonias that were documented by chest radiographs on 3 occasions. In 2006, she presented to a local hospital with headache, neck stiffness, photophobia, and altered mental status. Her cerebrospinal fluid (CSF) contained 3333 white blood cells (WBC)/ μ L (normal, 0-5 WBC/ μ L) with 95% lymphocytes, 22 red blood cells (RBC)/ μ L (normal, 0 RBC/ μ L), 114 mg of protein/dL (normal, 14-45 mg/dL), and 57 mg of glucose/dL (normal, 44-100 mg/dL). She was treated for bacterial meningitis and made a full recovery. Six months after this episode, she was hospitalized for mental status changes and was treated for HSVE because of a positive result on HSV PCR of her spinal fluid. She was referred to the University of Colorado Immunology Clinic after serum immunoglobulin values were noted to be low.

Her laboratory studies are summarized in Table I. Preimmunization and postimmunization antibody titers showed no responses to tetanus toxoid, diphtheria toxoid, or any of 14 pneumococcal serotypes. Based on these clinical and laboratory results, she was given a diagnosis of CVID and started on intravenous immunoglobulin (IVIG). Since beginning treatment, she has not experienced any infectious complications and has not required any form of antimicrobial treatment.

Patient 2. Patient 2 was a 42-year-old white man who was transferred from an outside hospital after experiencing tonic-clonic seizures. He then had fever and headache and was admitted to an outside hospital. CSF studies showed 86 WBC/ μ L with 94% lymphocytes, 15 RBC/ μ L, and 112 mg of protein/dL. HSV was identified by means of PCR of the CSF. The patient had a complicated hospital course and was transferred to the University of Virginia Hospital for further management. His past medical history included frequent bouts of acute sinusitis, multiple documented pneumonias over the previous 4 years, and an episode of varicella zoster infection during early adulthood. Physical examination on arrival demonstrated obtundation with minimal response to verbal commands, generalized hyperreflexia, and generalized clonus. Immune studies are summarized in Table I.

He was treated with acyclovir. He also had spiking fevers and was treated with piperacillin/tazobactam and vancomycin for hospital-acquired pneumonia, *Clostridium difficile*-induced enteritis that was treated with metronidazole, and pulmonary embolism for which he was started on long-term anticoagulation. The patient was continued on acyclovir, and by discharge, his mental status had improved significantly. He has continued to receive IVIG and 3 years later remains free of serious infections, including pneumonia.

TABLE I. Clinical laboratory data

Parameter (normal range)	Patient 1	Patient 2	Patient 3
Serum IgG (751-1,560 mg/dL)	<60 mg/dL	<100 mg/dL	<33 mg/dL
Serum IgM (46-453 mg/dL)	13 mg/dL	17 mg/dL	27 mg/dL
Serum IgA (46-304 mg/dL)	<4 mg/dL	40 mg/dL	<7 mg/dL
Serum IgE (0-100 IU/mL)	<1 IU/mL	ND	ND
CD3 ⁺ cells (857-3112/ μ L)	1305/ μ L	934/ μ L	1015/ μ L
CD4 ⁺ cells (511-2245/ μ L)	960/ μ L	520/ μ L	586/ μ L
CD8 ⁺ cells (258-1394/ μ L)	300/ μ L	390/ μ L	408/ μ L
CD19 ⁺ cells (135-711/ μ L)	30/ μ L	142/ μ L	10/ μ L
IgD ⁺ /CD27 ⁺ B cells*	4.3%	ND	ND

*Isotype-switched memory B cells (normal range, 8% to 40%).

Patient 3. Patient 3 was a 25-year-old man who presented to an outside hospital with a 12-hour history of delirium and combative behavior. He was transferred to the University of Virginia for further evaluation. The patient's past medical history included an episode of bacterial meningitis 3 years before (unknown organism), as well as 7 documented pneumonias in the previous 8 years.

On examination, the patient was somnolent and only arousable to loud voices and was noted to have right upper extremity rigidity and right greater than left bilateral lower extremity clonus. The CSF contained 2060 WBC/ μ L with 84% lymphocytes/ μ L, 240 RBC/ μ L, 123 mg of protein/dL, and 53 mg of glucose/dL and showed a positive PCR result for HSV. Given the history, the patient had immunoglobulins measured that showed hypogammaglobulinemia (Table I). He was treated with acyclovir and continued on IVIG. At discharge, the patient was noted to have severe Wernicke aphasia and significant cognitive impairment.

Approximately 1 month after discharge, the patient became increasingly agitated and febrile and was readmitted to the hospital. The CSF showed 50 WBC/ μ L with 94% lymphocytes, 0 RBC/ μ L, 117 mg of protein/dL, and 53 mg of glucose/dL. CSF results were negative for HSV and echovirus by means of PCR, HSV culture, and *Cryptococcus* species antigen. It was concluded that this was reactivation of HSVE, and the patient received an additional 3 weeks of intravenous acyclovir.

Over the next several months, the patient had a chronic productive cough. A chest computed tomographic scan showed enlarged hilar and mediastinal lymph nodes and small non-calcified nodules in the lateral aspect of the right upper lobe but no evidence of bronchiectasis. Also noted was a 27 $\times$ 16-mm soft tissue mass in the anterior mediastinum that was not present on any of his previous images. The patient subsequently underwent a transsternal removal of a thymoma. Although CVID was a logical initial diagnosis, in retrospect this patient might have Good syndrome, which has variously been viewed as a subset of CVID or a distinct clinical entity.¹ We include this case because the clinical presentations, diagnostic criteria, and treatments of the shared underlying immune disorder are similar.

CVID is characterized by decreased qualitative and quantitative immunoglobulin levels, resulting in infections, most often by bacterial pathogens.¹ The frequent concurrence of defects in T-cell immunity also predisposes patients to disseminated viral infections, particularly with herpes viruses, and to systemic fungal infections. The striking aspect of our cases was the finding of HSVE presenting in an illness most often associated with

bacterial pathogens. The question in these cases is whether the antibody deficiency caused by CVID predisposed these patients to HSVE.

HSV is extremely common in the general population, yet resultant encephalitis is rare. Murine studies have demonstrated that antibodies play a role in the immune system's response to viral infections. Studies in B cell-deficient mice have shown increased susceptibility to HSVE.² After mice are inoculated with HSV, administration of protective antibody decreases titers of virus in the liver and brain and provides protection against the spread of virus in both the central and peripheral nervous systems.^{3,4} In mice with both B-cell and T-cell impairments, administration of protective antibody prolongs survival.⁵

In human subjects with hypogammaglobulinemia, there are multiple case reports of encephalomyelitis with viruses such as West Nile virus, JC virus, enterovirus, poliovirus, and cytomegalovirus. As far as we know, ours are the first documented cases of HSVE as the presenting diagnosis in CVID.

None of our patients were receiving IVIG when the diagnosis of CVID was made, and it is likely that the development of the HSVE was a consequence of delayed recognition of hypogammaglobulinemia and institution of antibody-replacement therapy. IVIG provides sufficient HSV-specific IgG to neutralize or opsonize virus. However, current understanding is that HSV persists in neural ganglia, and HSVE reflects neural transmission into the central nervous system, a mechanism unlikely to be modulated through these mechanisms. However, antibodies also act to enhance antigen uptake by dendritic and other antigen-processing cells and thereby render antiviral cellular immunity and cytotoxic cell activation, mechanisms more relevant to protection against HSVE.

The presentation of CVID with HSVE raises the questions of whether these patients represent a distinct form of CVID. Recent studies analyzing patients with CVID have identified distinct cohorts, including those presenting with opportunistic infections, and found that these patients had a higher prevalence of splenomegaly, granuloma, enteropathy, and lymphoma and were more likely to have a history of consanguinity. It was suggested that these patients, possibly consistent with ours, might comprise a distinct clinical phenotype having late-onset combined immune deficiency and distinguished by the concomitant presence of profoundly defective T-cell function.⁶ There are also abnormalities in innate immunity that selectively predispose infants to HSVE, including mutations affecting responses by the viral molecular pattern receptors Toll-like receptor (TLR) 3 and TLR9, as well as the TLR3 adapter protein UNC-93B.⁷⁻⁹ Older children who survived these infections in infancy appear to be resistant to repeated infections, possibly because of development of adequate adaptive immunity against the virus. We speculated that

susceptibility to HSVE in our patients reflected hypomorphic mutations of function of these peptides that only became clinically significant in the presence of antibody deficiency. However, when PBMCs from patients 1 and 2 were stimulated with ligands for TLR3 and TLR9 and secreted TNF- α levels were measured, their responses were comparable with those of normal control cells, suggesting this was not the case.

In summary, most cases of hypogammaglobulinemia present with recurrent bacterial infections, as was the case in all 3 of our patients before their presentation with HSVE. The low prevalence of CVID combined with the protective treatment of these patients with IVIG makes finding the true incidence difficult. However, it is likely that untreated patients are primarily at increased risk for viral infections, including the catastrophic diagnosis of HSVE.

Larry Borish, MD^a

Andrew G. Ayars, MD^b

Charles H. Kirkpatrick, MD^b

From ^athe Asthma and Allergic Disease Center, University of Virginia Health Systems, Charlottesville, Va, and ^bthe Division of Allergy and Clinical Immunology, University of Colorado Health Sciences Center, Aurora, Colo. E-mail: lb4m@virginia.edu.

Supported by National Institutes of Health grants RO1-AI47737 and PO1-AI50989.

Disclosure of potential conflict of interest: C. H. Kirkpatrick has provided legal consultation/expert witness testimony in cases related to human growth hormone in HIV infections and is on the Advisory Board for CSL Behring. The rest of the authors have declared that they have no conflict of interest.

REFERENCES

1. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol* 2005;94(suppl 1):S1-S63.
2. Beland JL, Sobel RA, Adler H, Del-Pan NC, Rimm JJ. B cell-deficient mice have increased susceptibility to HSV-1 encephalomyelitis and mortality. *J Neuroimmunol* 1999;94:122-6.
3. Buchmeier M, Lewicki H, Talbot P, Knobler R. Murine hepatitis virus-4 (strain JHM)-induced neurologic disease is modulated in vivo by monoclonal antibody. *Virology* 1984;132:261-70.
4. Dix RD, Pereira L, Baringer JR. Use of monoclonal antibody directed against herpes simplex virus glycoproteins to protect mice against acute virus-induced neurologic disease. *Infect Immun* 1981;34:192-9.
5. Minagawa H, Sakuma S, Mohri S, Mori R, Watanabe T. Herpes simplex virus type 1 infection in mice with severe combined immunodeficiency disease (SCID). *Arch Virol* 1988;103:73-82.
6. Malphettes M, Gérard L, Carmagnat M, Mouillot G, Vince N, Boutboul D, et al. Late-onset combined immune deficiency: a subset of common variable immunodeficiency with severe T cell defect. *Clin Infect Dis* 2009;49:1329-38.
7. Casrouge A, Zhang SY, Eidenschenk C, Jouanguy E, Puel A, Yang K, et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. *Science* 2006;314:308-12.
8. Zhang SY, Jouanguy E, Ugolini S, Smahi A, Elain G, Romero P, et al. TLR3 deficiency in patients with herpes simplex encephalitis. *Science* 2007;317:1522-7.
9. Cunningham-Rundles C, Radigan L, Knight AK, Zhang L, Bauer L, Nakazawa A. TLR9 activation is defective in common variable immunodeficiency. *J Immunol* 2006;176:1978-87.

doi:10.1016/j.jaci.2010.11.004