Published in final edited form as:
J Allergy Clin Immunol. 2011 February ; 127(2): 541–543. doi:10.1016/j.jaci.2010.11.004.

Common Variable Immunodeficiency Presenting as Herpes Simplex Encephalitis

Larry Borish, MD[2], **Andrew G Ayars, MD**[1], and **Charles H Kirkpatrick, MD**[1]

[1] Division of Allergy and Clinical Immunology, University of Colorado Health Sciences Center, Aurora, CO 80045

[2] Asthma and Allergic Disease Center, University of Virginia Health Systems, Charlottesville, VA 22908

Summary

Common variable immunodeficiency (CVID) is a disorder in which patients are unusually susceptible to infections with encapsulated bacteria. Here we describe three adults with CVID in whom the correct diagnosis was not reached until they had Herpes simplex encephalitis. Failure to identify the underlying immune deficiency likely contributed to these debilitating infections.

Keywords

Common variable immunodeficiency; Herpes simplex encephalitis; anti-viral antibodies

To the Editor

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders with the common endpoint 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 viral (HSV) encephalitis. These are the first described cases of CVID presenting with HSV encephalitis (HSVE).

Patient #1

Patient #1, a 54 year old female, with a past history of pneumonias that were documented by chest x-rays on three occasions. In 2006, she presented to a local hospital with headache, neck stiffness, photophobia and altered mental status. Her cerebral spinal fluid (CSF) contained 3333 WBC/μl (normal = 0–5/μl) with 95% lymphocytes, 22 RBC/μl (normal = 0), 114 mg of protein/dl (normal = 14–45 mg/dl) and 57 mg of glucose/dl (normal = 44–100

[2]To whom correspondence should be addressed at: Asthma and Allergic Disease Center, University of Virginia Health System, Charlottesville, VA 22908, Tel # (434) 243 6570; fax # (434) 924 5779, lb4m@virginia.edu.
Larry Borish, M.D., Asthma and Allergic Disease Center, University of Virginia Health Systems, Charlottesville, VA 22908
Andrew G. Ayars, M.D., Division of Allergy and Clinical Immunology, University of Colorado Health Sciences Center, Aurora, CO 80045
Charles H. Kirkpatrick, M.D., Division of Allergy and Clinical Immunology, University of Colorado Health Science Center, Aurora, CO 80045

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 Herpes simplex encephalitis because of a positive HSV-polymerase chain reaction (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. Pre- and post- immunization 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 diagnosed with CVID and started on IVIG. Since beginning treatment she has not experienced any infectious complications and has not required any form of antimicrobial treatment.

Patient #2

Patient #2 is a 42 year old white male who was transferred from an outside hospital after developing tonic-clonic seizures. He then developed fever and headache and was admitted to an outside hospital. CSF studies showed 86 WBC/μL with 94% lymphocytes, 15 RBC/μL, and 112 mg protein/dL. HSV was identified by 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 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* 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 remained on IVIG and 3 years later remains free of serious infections including pneumonia.

Patient #3

Patient #3, a 25 year old male, 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 prior (unknown organism) as well as seven documented pneumonias in the previous 8 years.

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

Approximately one month after discharge the patient became increasingly agitated, febrile and was readmitted to the hospital. The CSF showed 50 WBC/μL with 94% lymphocytes, 0 RBC/μL, 117 mg of protein/dl and 53 mg of glucose/dl. CSF was negative for HSV and echovirus by PCR, HSV culture, and Cryptococcus antigen. It was concluded that this was reactivation of HSV encephalitis and the patient received an additional 3 weeks of IV acyclovir.

Over the next several months the patient developed a chronic productive cough. A chest CT showed enlarged hilar and mediastinal lymph nodes, small non-calcified nodules in the lateral aspect of the right upper lobe, but no evidence of bronchiectasis. Also noted was a 27 × 16 mm soft tissue mass in the anterior mediastinum that was not present on any of his previous images. The patient subsequently underwent a trans-sternal removal of a thymoma. While CVID was a logical initial diagnosis, in retrospect this patient may have Good's 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 lowers titers of virus in the liver and brain and provides protection against 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 humans with hypogammaglobulinemia there are multiple case reports of encephalomyelitis with viruses such as West Nile virus, JC virus, enterovirus, poliovirus and CMV. As far as we know, ours are the first documented cases of HSVE as the presenting diagnosis in CVID.

None of our patients were on 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 CNS – a mechanism unlikely to be modulated through these mechanisms. But 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, may 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 TLR3 and TLR9, as well as the TLR3 adapter protein UNC-93B[7, 8, 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 hypomorphous mutations of function of these peptides that only became clinically significant in the presence of antibody deficiency. However, when peripheral blood mononuclear cells from cases 1 and 2 were stimulated with ligands for TLR3 and TLR9, and secreted TNF-α measured, their responses were comparable to the 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 prior to 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 the ones at increased risk for viral infections including the catastrophic diagnosis of HSVE.

Acknowledgments

Supported by NIH grants RO1-AI47737 and PO1-AI50989

Abbreviations

CMV	cytomegalovirus
CVID	common variable immune deficiency
CSF	cerebral spinal fluid
HSV	herpes simplex virus
HSVE	herpes simplex virus encephalitis
IVIG	intravenous immunoglobulin
PCR	polymerase chain reaction

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Table 1

Clinical Laboratory Data

Parameter (normal range)	Patient 1	Patient 2	Patient 3
Serum IgG (751–1560 mg/dl)	<60 mg/dl	<100 mg/dl	<33 mg/dl
Serum IgM (46–453 mg/dl)	13 mg/dl	17 mg/dl	27mg/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	N.D.	N.D.
CD3+ (857–3112/μl)	1305/μl	934/μl	1015/μl
CD4+ (511–2245/μl)	960/μl	520/μl	586/μl
CD8+ (258–1394/μl)	300/μl	390/μl	408/μl
CD19+ (135–711/μl)	30/μl	142/μl	10/μl
IgD-/CD27+ B-cells[1]	4.3%	N.D.	N.D.

[1] Isotype-switched memory B-cells (normal range 8–40%)