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ORIGINAL ARTICLE

Neurologic Complications of Common Variable Immunodeficiency

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Abstract Common variable immunodeficiency is a rare disorder of immunity associated with a myriad of clinical manifestations including recurrent infections, autoimmunity, and malignancy. Though rare, neurologic complications have been described in a small number of case reports and case series of CVID patients. In this article, we present a patient with CVID who suffered significant neurologic morbidity and categorize the reported range of neurologic complications associated with CVID. Our case highlights the complex nature of neurologic manifestations in CVID patients, and our review of the current database suggests that infection and inflammatory neurologic disorders are the cause of most neurologic presentations.

Keywords Common variable immunodeficiency · Neurologic disease · Autoimmune

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Introduction

Common variable immunodeficiency (CVID) is a rare disorder of immunity characterized by hypogammaglobulinemia, impaired specific antibody responses, and variable T lymphocyte dysfunction. It can occur in both children and adults but is most commonly diagnosed in early adulthood. Although CVID is commonly associated with recurrent infections, other systemic conditions, such as autoimmunity, inflammatory disorders, and malignancy, have been well described [1].

Neurologic dysfunction in CVID is less frequently reported, and the relationship to underlying immune dysfunction is not well understood. Current knowledge is based mostly upon case reports or small case series. In this article, we present a patient with CVID who suffered significant neurologic morbidity, we categorize the reported range of neurologic complications associated with CVID, and we highlight some of the diagnostic and treatment challenges faced by clinicians who care for these complex patients.

Case

A 40-year-old woman with CVID developed neurologic and ophthalmologic symptoms in 2009. Her complex history includes a diagnosis of CVID in 2007, with lymphocytic interstitial pneumonia (LIP), for which she was treated with mycophenolate mofetil (MM) with good benefit. Subsequently, she developed lymphocytic colitis, and after attempting multiple therapies without success, she was begun on adalimumab, which was associated with excellent improvement of her diarrhea. MM was discontinued for a brief time during this treatment but restarted after decompensation of her LIP, which again stabilized.

In August of 2009, she experienced subacute onset of blurry vision in her left eye that was associated with several weeks

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of retro-orbital pain. She was given a 3-day course of methylprednisolone for presumed optic neuritis with improvement in her vision after 3 weeks from a visual acuity of 20/400 to 20/25. She was left with a mild residual left cecocentral scotoma that has been unchanged since that time with surveillance monitoring by her neuro-ophthalmologist. Several months later, she developed multifocal choroidopathy, which was suspected to be inflammatory in origin. Subsequent retinal evaluations over the intervening years showed no progression.

In July of 2013, she presented with 6 weeks of episodic visual distortion and headaches. On fundoscopic exam, she had persistent multifocal choroidopathy, left optic disc pallor, and nerve atrophy consistent with her prior ophthalmologic history. Cerebrospinal fluid (CSF) analysis demonstrated lymphocytic pleocytosis with 34 WBCs, mildly elevated protein, and greater than five oligoclonal bands. VDRL, VZV PCR, and Lyme IgM/IgG were all negative (Table 1). MRI of her brain, cervical, and thoracic spine were unrevealing. Peripapillary optical coherence tomography showed mild retinal nerve fiber layer loss (87 μ OS versus 93 μ OD) with modest but more significant loss of macular volume suggestive of some permanent ganglion cell loss. The precise etiology of her inflammatory CSF and neurologic symptoms remained unclear.

In February of 2014, she developed new weakness of her left hand, along with tremor and poor coordination. She was found to have left-sided dysmetria and an unchanged ophthalmologic exam. Brain MRI demonstrated two enhancing lesions with mild mass effect in the left cerebellum (Fig. 1a). Repeat lumbar puncture (LP) showed similar CSF parameters except for the presence of low numbers of neutrophils (Table 1). Histological analysis with two brain biopsies showed modest astrogliosis (confirmed via glial fibrillary acid protein immunohistochemistry) with superimposed nonspecific inflammation including otherwise normal architecture. Specifically, there was no evidence for myelin injury or loss. There was a modest lymphocytic infiltration with predominantly T cells (CD3+) and scant CD20+ cells. There were no granulomas identified and no tissue necrosis or viropathic changes seen (Table 2). Extensive infectious work-up, including research-based metagenomic deep sequencing (MDS) of her CSF and brain tissue for the identification of potential pathogens revealed no specific etiology (Fig. 2).

In October of 2014, the patient experienced a syncopal episode while running on a treadmill, which was followed by postictal confusion. A repeat MRI demonstrated persistence of the cerebellar lesions as well as new ill-defined areas of leptomeningeal enhancement, proximate to the right angular gyrus, which was thought to serve as the seizure focus (Fig. 2d). She was started on levetiracetam without any seizure recurrence. Repeat CSF analysis continued to demonstrate signs of inflammation (Table 1).

Given concern for infection in the setting of immunosuppression, or possible atypical demyelination, adalimumab was discontinued. At this time, she continued to have left arm dysmetria along with new subtle imbalances brought out by complex tasks (at baseline the patient was a high level endurance athlete). Neuropsychiatric testing demonstrated relatively focal impairment in word retrieval. Understanding the small risk that her condition might be infectious in nature, she was given 3 days of methylprednisolone and experienced rapid improvement in balance, fine motor movement, short-term memory, and word finding. MRI obtained shortly thereafter demonstrated interval decrease in the prominence of leptomeningeal enhancement about the bilateral superior cerebellar hemispheres and right angular gyrus (Fig. 1e). A brain MRI obtained 2 months later, however, demonstrated an expansile lesion with increased T2 signal abnormality and gadolinium enhancement involving the medial aspect of the right posteroinferior cerebellar lobe (Fig. 1f).

Based upon her CSF results, lack of evidence for infection, and good response to corticosteroids, rituximab was added to

Table 1 Serial CSF analysis

CSF studies	7/29/13	2/25/14	3/4/14	Reference ranges
WBC	34	30	4	0–5/cc
Poly		2 %		%
Lymph	74 %	78 %	86 %	%
RBC	5	4	none	/cc
Glucose	41	40	47	40–70 mg/dl
Blood glucose	75	77	85	mg/dl
Protein	66	51	42	15–50
IgG	3.7	2.9	3	0.3–4.3
Micro	VZV PCR, VDRL, Lyme Ab negative	VDRL NR		
IgG index	0.5	0.5	0.5	0.3–0.6
OCB	>5	>5	>5	
Cytology	Mature lymphocytes and monocytes			

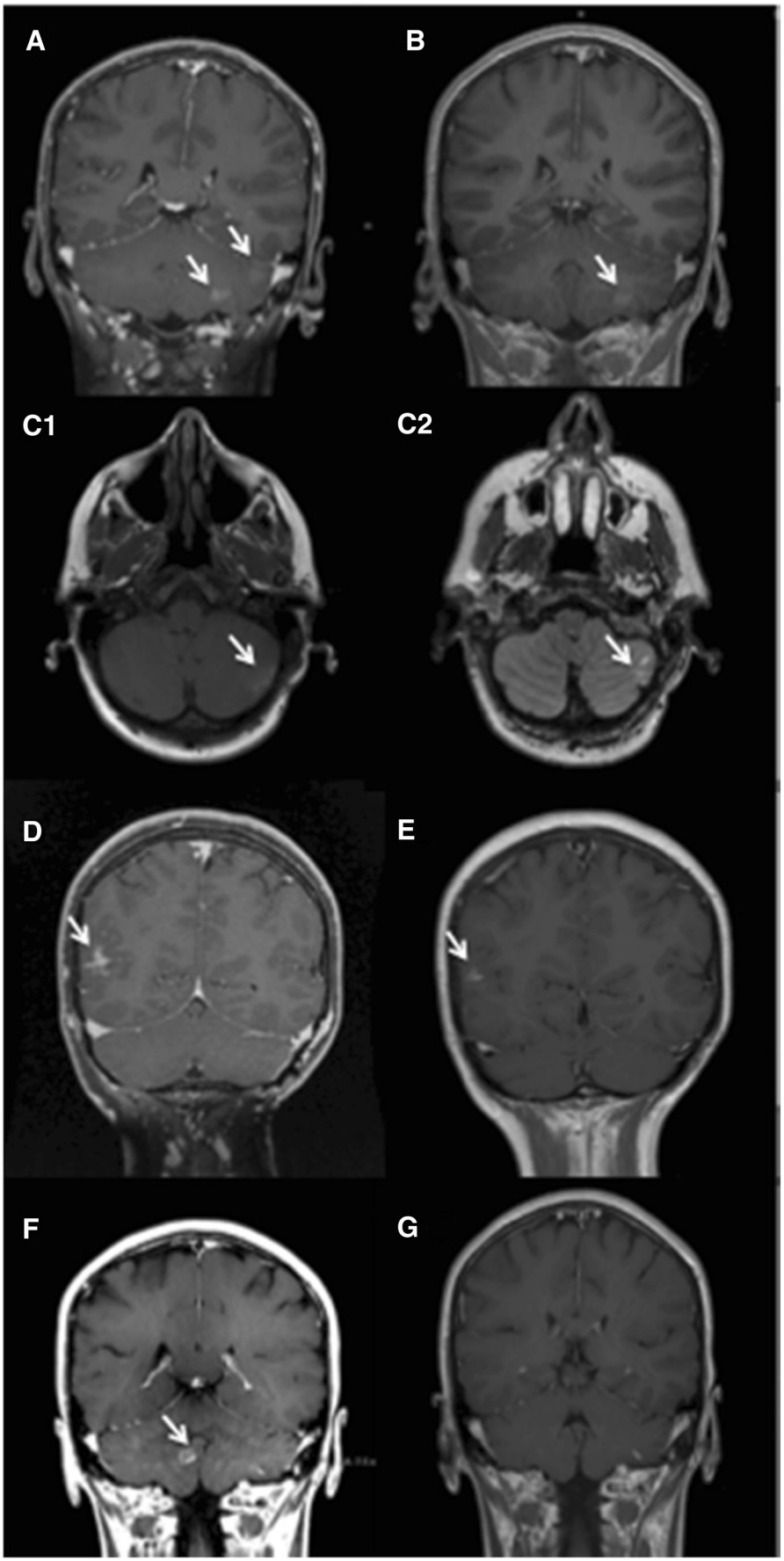

Fig. 1 Serial MRI brain images. **a** 2/2014 Two new enhancing lesions with mild mass effect in the left cerebellum on T1 post-gadolinium imaging (*white arrows*). **b** 4/2014 Near-complete resolution of left superior cerebellar hemispheric lesion. Unchanged left inferior cerebellar lesion (*white arrow*). **c** 5/2014 Increased conspicuity of leptomeningeal enhancement along the dorsal left paramedian cerebellum. Stable ill-defined enhancement (**c1**) and FLAIR hyperintensity associated with the inferior left cerebellar lesion (**c2**). **d** 10/2014 New ill-defined areas of enhancement principally confined to the leptomeninges and proximate right angular gyrus (*arrow*). **e** 11/2014 Interval decreased contrast enhancement about a left dorsal lateral cerebellar intraparenchymal lesion (not pictured), bilateral superior cerebellar hemisphere sulci (not pictured), and sulcus proximate to the right angular gyrus (*arrow*). **f** 1/2015 Edematous lesion with increased signal abnormality and enhancement involving the medial aspect of the right posterioinferior cerebellar lobe. Previously seen mild leptomeningeal enhancement along the right angular gyrus was slightly decreased in conspicuity. **g** 3/2015 Interval decrease in conspicuity of leptomeningeal enhancement involving the right angular gyrus and right posterior inferior cerebellar lobe. No new areas of enhancement

Table 2 Pathology from brain biopsy

Final pathologic diagnosis
A. Cerebellum, biopsy: Cerebellar cortex with minimal astrogliosis
B. Cerebellum, biopsy: Cerebellar cortex no significant pathologic abnormality.
C. Cerebellum, "snap freeze," biopsy: Cerebellar cortex with no significant pathologic abnormality.
D. Cerebellum, "lesional tissue," biopsy: Cerebellar cortex,with sparse population of lymphocytes,see comment.
E. Cerebellum, "white matter," biopsy: Cerebellar cortex with no significant pathologic abnormality.
F. Cerebellum, biopsy: Cerebellar cortex with no significant pathologic abnormality.
G. Dura, biopsy: Cerebellum with adjacent fibrovascular tissue.

Multiple biopsies of predominately cerebellar cortex are reviewed, most of which demonstrate normal cerebellar cortex. Immunohistochemistry revealed CD45+ lymphocytes in cerebellar lesional tissue; GFAP staining did not show prominent astrogliosis and only a few microglia (CD68+). No foci of necrosis or associated macrophage infiltrate was seen

her regimen. Repeat MRI after four doses (650 mg once weekly) demonstrated interval resolution of the cerebellar lesions and decrease in leptomeningeal enhancement, without new areas of enhancement (Fig. 1g). Since the addition of rituximab (now three courses) and discontinuation of adalimumab, she has remained neurologically stable with near-complete resolution of previous symptoms (Fig. 1g).

Neurologic Manifestations of CVID

To better understand our patient's case, we turned to the literature but found a paucity of useful information. We therefore carried out a comprehensive web-based search, regardless of publication status or language, using PubMed, Web of Science, and Google Scholar databases to identify all articles that examined the association between neurological diseases and CVID. Various neurologic terms were used in different combinations. A cited references search of retrieved articles was carried out. This information is summarized in Table 3.

Categories of Neurologic Complications

Infectious etiologies comprise the largest category of reported neurologic complications, with a total of 43 case reports. Notably, the variety of infections is broad, including bacterial, fungal, and viral, with six patients with reported progressive multifocal leukoencephalopathy (PML) [3–8]. Three patients with HSV encephalitis were diagnosed as adults [9].

Several themes emerge from scrutinizing these cases. First, bacterial meningitis accounted for about half of the infections and was often the presenting manifestation of CVID. As one might anticipate, *Streptococcus pneumoniae* was the major source of bacterial meningitis. Other organisms included *N. meningitidis*, *S. aureus*, *E. coli*, *H. influenzae*, *Listeria*, and *Pseudomonas*, with the majority of cases reflecting a similar spectrum of bacteria isolated in the general population [1].

Second, more than half of the PML patients and several others required CNS biopsy for diagnosis. Third, many of the infections occurred before diagnosis of CVID, and the doses and route of IgG administration are seldom recorded.

Autoimmune/inflammatory conditions comprise the next largest category of neurologic complications. There are 13 reported cases of "myelitis" with a mean age at diagnosis of 31, and a broad range from 1 to 71. The many and varied clinical presentations included motor weakness, paresthesias, sensory loss, and urinary retention. All patients were treated with either corticosteroids or TNF alpha inhibitors, and achieved stabilization or resolution of their symptoms. One patient had extensive transverse myelitis that responded well to a 3-day course of high-dose IV methylprednisolone and initiation of IVIg [10]. Similarly, another patient had multiple relapses of myelitis that had been treated with glucocorticoids.

Metagenomic Deep Sequencing Protocol

The surplus CSF (i.e., 250 uL) and brain tissue (<50 mg) were submitted for unbiased MDS under a research protocol for the identification of potential pathogens (i.e., RNA and DNA viruses, fungi, parasites and bacteria) approved by the Institutional Review Board of the University of California, San Francisco. Total RNA was extracted from both tissue types, and random hexamer primers were used to reverse transcribe the RNA. Double stranded complementary DNA next-generation sequencing libraries were generated and sequenced on an Illumina HiSeq 2500 machine (Illumina, San Diego, CA).[2]

In total, 59,219,136 and paired-end 135 base pair (bp) sequences were obtained from the brain biopsy specimen, and 40,483,558 sequences were obtained from RNA extracted from the CSF. The sequences were processed through a rapid custom bioinformatics pipeline that involves quality filtering, iterative removal of sequences that align to the human genome and removal of low complexity and redundant sequences. After these steps, only 427 (0.0007%) and 6,621 (0.02%) sequence read pairs remained from the brain biopsy and CSF datasets, respectively. These remaining unique, complex and non-human sequences were classified to identify potential pathogens by comparing them to the entire National Center for Biotechnology Information's nucleotide reference database.[2] In both tissues, only common skin flora and reagent contaminants were identified.

Fig. 2 UCSF metagenomic deep sequencing protocol for identification of potential pathogens

Table 3 Neurologic Complications of CVID

Infectious (43)
Adenovirus meningoencephalitis (2) [25]
Bacterial meningitis (22) [1, 26–29]
BKV encephalitis and optic neuritis (1) [30]
CMV encephalomyelitis (1) [31]
Echovirus meningoencephalitis (1) [25]
Histoplasmosis (1) [28]
HSV encephalitis (3) [9]
Mumps encephalitis (1)
Poliovirus (1) [32]
Progressive Multifocal Leukoencephalopathy (6) [3–8]
Toxoplasma encephalitis (2) [33, 34]
Varicella angiitis (1) [35]
Varicella zoster encephalitis (1) [1]
West Nile meningitis (1) [36]
Autoimmune/Inflammatory (13)
optic neuritis (1) [37]
myelitis (4) [10, 11, 38, 39]
limbic encephalitis (1) [12]
Guillian Barre Syndrome (1) [40]
granulomatous mass (4) [41–44, 45]
chronic inflammatory demyelinating polyneuropathy (1) [39]
acute disseminated encephalomyelitis (2) [14, 46]
Unknown etiology (10)
encephalopathy (4) [47]
myelopathy (2) [47]
polyneuropathy (1) [48]
progressive neurodegenerative disease (3) [20]
retinopathy (1) [47]
Endocrine (3)
partial central DI (1) [16]
isolated ACTH deficiency (1) [17]
GH deficiency (1) [15]
Nutrient deficiency (3)
subacute combined degeneration (1) [19]
vitamin E (2) [18]

Parenthesis indicates number of cases

She had no further recurrences after switching to high-dose subcutaneous immunoglobulin G replacement therapy [11]. Ten noninfectious cases of encephalopathy are described, three of which are associated with inflammation, while six are of unclear etiology (Table 3).

One patient with "limbic encephalitis" and two patients with acute encephalomyelitis saw improvement upon treatment with corticosteroids and infliximab, respectively [12–14]. The patient with "limbic encephalitis" like syndrome suffered recurrent symptoms twice when the corticosteroids were tapered. CVID was eventually diagnosed in conjunction with the presence of high anti-GAD antibodies in the serum and CSF (which is typically associated with cerebellitis and stiff person syndrome) [12].

Neuroendocrine disorders were reported in three patients. Interestingly, these cases may have been complications of autoimmune hypophysitis. Growth hormone deficiency, diabetes insipidus, and isolated ACTH deficiency were treated successfully with hormone replacement. Antipituitary antibodies were found in one patient, consistent with previous observations in patients with idiopathic hormonal deficiencies. All of these patients exhibited normal imaging [15–17].

Nutritional deficiencies were reported in three patients with neurologic manifestations, two with vitamin E deficiency, and one with vitamin B12 deficiency [18, 19]. The vitamin E-deficient patients presented with tremors, paresthesias, and unsteadiness, and had bland CSF analysis and MRIs with extensive high signal changes in the white matter of the frontal and parietal lobes. Improvement in symptoms was observed in both patients after supplementation, though one continued to have persistent MRI findings. These nutrient deficiencies were postulated to have arisen from CVID-associated enteropathy. The case of vitamin B12 deficiency was associated with a high concentration of anti-parietal cell antibodies.

Lastly, in 2002, Ziegner et al. reported several cases of progressive neurodegeneration in patients with primary immunodeficiency who were receiving immunoglobulin replacement therapy [20]. It was speculated whether use of IVIg might be playing a role in these cases. In the current review, we found no additional evidence that would support IVIg as a cause of progressive neurodegeneration in patients with CVID.

Discussion

Our patient's case highlights multiple themes in the care of CVID patients who exhibit neurologic signs of disease. The clinical manifestations are many and varied, depending on what part of the CNS is involved and contingent upon the underlying etiology.

The role of immunoglobulins in fighting infection is complex. Although we normally think of humoral immunity as being essential to prevent and treat mucosal bacterial infections, IgG can also opsonize or neutralize viruses, and it plays a role in the stimulation of cell-mediated immunity. Mouse models have demonstrated protective effects of IgG on the central and peripheral nervous systems of mice inoculated with HSV [9]. The variety of CVID associated viral CNS infections in humans is impressive. Notably, for patients with chronic enteroviral meningoencephalitis, the current primary immunodeficiency practice parameter recommends enough supplemental IgG to achieve a trough level >1000, implying that higher serum levels might improve outcomes [21]. In general, however, the benefit of higher or more frequent dosing of IgG for viral illnesses associated with CVID is not well investigated. Multiple other factors, such as environmental

exposures, host vulnerability, and degree of T lymphocyte dysfunction, undoubtedly contribute to whether a given individual experiences clinical infection.

Our patient's case also highlights the challenge of distinguishing between CNS infection and autoimmune/inflammatory disease. Given that the treatment for autoimmune disease is immunosuppression (of various sorts), correct diagnosis is imperative for these immunocompromised patients. Serologic diagnosis is problematic in patients who are already receiving IgG. Evaluation of CSF fluid can be diagnostic, but biopsy of the CNS may be required.

Our patient was ultimately determined by biopsy to have no evidence of infection, and her existing multiple autoimmune conditions supported an autoimmune etiology of her neurologic disease. Novel neuronal auto-antibodies were not assessed in CSF or serum from this patient. Although the patient did not exhibit a syndrome consistent with meningoencephalitis caused by an identified CNS-targeted antibody, further evaluation could include research assessments for previously unidentified antibodies. We also did not feel that the character and pattern of her deficits including her degree of clinical recovery were consistent with a diagnosis of neuromyleitis optica.

B12 deficiency should be considered in any patient with CVID and neurologic findings, particularly those patients with significant gastrointestinal disease. Our patient's serum B12 level was normal, and although methylmalonic acid and serum homocysteine levels were not assayed, the expansile-enhancing brain lesions with leptomeningeal enhancement and CSF pleocytosis were not consistent with B12 deficiency.

To complicate the clinical challenge in determining the cause of neurological deficits in patients such as ours with CVID, there have been case reports of inflammatory CNS disorders associated with the use of anti-TNFα agents. Such conditions include optic neuritis, Guillian Barre, and others [22]. In one trial of 77 patients, three of the patients developed anti-TNFα-associated demyelination and all had resolution of symptoms after discontinuing these agents for 2–3 months—the biological significance of these findings, however, is uncertain [22].

Our patient had been taking adalimumab at the onset of her neurologic symptoms. However, she experienced improvement after a short course of corticosteroids, followed by radiologic and clinical deterioration more than 3 months after discontinuing adalimumab. It is therefore unlikely that adalimumab caused her neurologic pathology. Her biopsies were also inconsistent with inflammatory demyelination. Nevertheless, these reports of CNS inflammatory disorders associated with the use of anti-TNF alpha agents, which can play an important role in treating certain CVID-related conditions (such as refractory diarrhea in our patient), should be heeded by clinicians whose patients develop new neurologic findings.

With respect to our patient's other medications, we doubt that mycophenolate mofetil was responsible because the patient has continued on this agent (at even higher doses for her lymphocytic interstitial pneumonitis) without recurrence. Additionally, recent literature has provided reassurance regarding any connection between long-term use of MMF and neurologic toxicity [23, 24].

Fortunately, our patient's clinical and radiologic status has remained stable since the initiation of rituximab, implicating an autoimmune etiology for her neurologic manifestations.

Summary

Our patient's case highlights the complex nature of neurologic manifestations in CVID patients. Our review of the current database suggests that infection and inflammatory disorders are the cause of most presentations, and an autoimmune etiology should always be considered. Early and accurate diagnosis of CVID is important so that recognized treatments such as IVIg can be administered, but guidance regarding optimal dosing is lacking. The "infection" vs "inflammation" conundrum presents an important challenge to the physician who must select the best course of treatment.

Compliance with Ethical Standard

Conflict of Interest The authors declared that they have no conflict of interest.

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