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CD40 ligand Deficiency: Neurologic Sequelae with Radiographic Correlation

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Abstract

Patients with CD40 ligand deficiency are susceptible to central nervous system (CNS) infections, but existing reports have not detailed the neurologic progression or long-term outcome of CNS complications. Characterizing the CNS complications of immune deficiencies can result in the identification of new pathogens. We reviewed clinical data on patients with CD40 ligand deficiency who suffered neurodegeneration identified from a larger cohort of 31 patients. Five patients had progressive neurologic and cognitive decline in the absence of clinical signs of acute fulminant encephalitis, with anatomic brain abnormalities, and high mortality (60%). Despite multiple evaluations, pathogens were not identified in four patients, all of whom were on standard intravenous immune globulin therapy at illness presentation. This clinical phenotype of progressive decline without acute fulminant encephalitis is similar to chronic enteroviral encephalitis in X-linked agammaglobulinemia, another condition with severe humoral immune defects. Whether infection secondary to sub-therapeutic levels of CNS IgG, inadequately-protective levels of serum IgG, or impaired CD40 ligand-dependent IgG-independent antiviral responses contributed remains undetermined. Emerging gene-chip techniques applied in patients with primary immune deficiencies may identify hereto unknown viruses. Prospective neurocognitive and evaluation of patients with CD40 ligand deficiency may identify affected patients prior to overt clinical signs.

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Keywords

Encephalitis; Viral infections; CD40 ligand deficiency; X-linked hyper-IgM syndrome; neurodegeneration

Introduction

CD40 ligand deficiency is an uncommon primary immune deficiency with an estimated annual incidence of 1 in 10⁶ (1). CD40 ligand is preferentially expressed on activated CD4+ T cells and binds its cognate receptor, CD40, expressed on B cells, macrophages and antigen presenting cells [1,2]. CD40-CD40 ligand interactions are requisite for B cell immunoglobulin class switching [3], and to generate both memory B cells and physiologic macrophage and T cell responses to intracellular pathogens. Clinically, CD40 ligand deficiency is characterized by defects in cellular and humoral immunity resulting in a susceptibility to recurrent sinopulmonary bacterial infections and severe opportunistic infections. Patients are also susceptible to sclerosing cholangitis, which often results in cirrhosis and death, as well as inflammatory disorders and malignancies. Despite antibiotic prophylaxis and immune globulin replacement therapy, the survival rate at 25 years is only 20% [4–8].

Central nervous system (CNS) infections are frequently associated with primary immune deficiencies. CNS infections are known to occur in CD40 ligand deficiency, but the existing reports have not detailed the neurologic progression or long-term outcome of CNS complications [4–11]. Herein, we present the clinical findings and long-term neurologic sequelae of five patients with CD40 ligand deficiency who suffered progressive neurologic decline.

Methods

We reviewed the medical records of all patients with CD40 ligand deficiency enrolled in natural history protocols at the National Institute of Allergy and Infectious Diseases, National Institutes of Health and identified patients who underwent evaluation for neurologic decline. All patients enrolled in these protocols had molecular diagnoses of CD40 ligand deficiency using standard techniques. Patients underwent multiple evaluations at the NIH and outside institutions at various times after onset of neurologic symptoms by laboratory assessments, screening for infections, neurologic and ophthalmologic examinations, brain magnetic resonance imaging (MRI) or computed tomography (CT), electromyography (EMG) and electroencephalography (EEG) as clinically indicated. Cultured sites typically included the cerebral spinal fluid (CSF), upper and lower respiratory tracts, gastrointestinal tract, blood, stool and urine. Because multiple centers were involved, not every patient was screened for all pathogens at all sites at all times. Pathogens screened for included enteroviruses, cytomegalovirus, varicella zoster, herpes simplex-1 virus, influenza A and B, JC virus, *Cryptococcus neoformans*, *Borellia burgdorferi*, *Toxoplasma gondii* (*T. gondii*), fungi, mycobacteria and bacteria. Pathogens were assessed by polymerase chain reaction (PCR), gram and acid fast stains, culture, antibody/antigen studies and studies to evaluate fungi and yeasts. Viral pathogens were by assessed PCR, and in certain cases/sites, by culture also (e.g. stool). Brain MRI included non-contrast T1 and T2 weighted imaging and post-contrast T1 and fluid attenuation inversion recovery. Four patients were administered age-appropriate tests of cognitive function, including the Wechsler Adult Intelligence Scale, by clinical psychologists at the NIH to measure intelligence quotient (IQ). IQ was not obtained in one patient because of youth, but he did

undergo age-appropriate testing of cognitive and motor function. This study was approved by our institutional review board and all patients provided written informed consent.

Results

Case Histories

Patient 1 (P1) was born to unrelated parents. He was diagnosed at 12 months and remained healthy for 10 years after diagnosis on intravenous immune globulin but had neurologic decline starting at 11 years (Table 1). Cultures and imaging were not diagnostic (Table 2: Encounter 1, Fig 1A). High dose immune globulin did not improve his neurologic symptoms and he was discharged on immune globulin to maintain elevated trough levels. Three months later, he had a decline in neurologic function. CSF and MRI were abnormal, but remained non-diagnostic (Table 2: Follow up, Fig 1B). His neurologic disease significantly contributed to a respiratory infection to which he succumbed at 12 years (Table 1).

P2 was born to unrelated parents. He was diagnosed at 8 months and remained healthy for 5 years on immune globulin but had neurologic decline starting at 6 years (Table 1). Diagnostic studies, muscle and skin biopsies (to rule out myopathies and Ataxia-Telangiectasia) were normal. CSF was reported as normal but viral studies were not performed (Table 2: Encounter 1). High dose immune globulin did not improve his neurologic symptoms. EEG and MRI (Fig. 1C) were abnormal one year later, but CSF remained non-diagnostic and he continued on conventional immune globulin therapy. At 9 years, he was admitted for compassionate release pleconaril therapy [12]. He had symptom progression but CSF remained negative (Table 1, Table 2: Follow up). Pleconaril was ineffective and his decline progressed over the next three years despite immune globulin (Fig 1D). He died of neurologic disease at 14 years.

P3 was born to unrelated parents and was diagnosed at 14 months at which time he presented with ulcerative epiglottitis and was noted to have mild non-focal neurologic deficits and mild cerebral atrophy on CT, but CSF was not sampled (Table 1). He was treated for ulcerative epiglottitis and was placed on immune globulin. One month later, he presented with seizures and fever. CSF was not diagnostic and MRI and EEG were abnormal, but nonspecific (Table 2: Encounter 1). He developed some motor deficits one month after the seizures but appeared to be regaining his developmental milestones. He continues to be followed.

P4 was born to unrelated parents, and despite having two siblings with XHIM syndrome he was not diagnosed until 2 years. Despite immune globulin therapy starting at 2 years of age, he suffered recurrent infections over the following 16 years (Table 1). At 18 years, he presented with an insidious neurologic decline in the absence of signs of CNS or other infections. All evaluations were negative, however, and he was continued on immune globulin to maintain elevated trough levels. At 24 years, he presented for compassionate release pleconaril therapy (Table 1). Evaluation demonstrated elevated liver enzymes, abnormal MRI (Fig 1E) and EEG, and CSF with minimal lymphocytosis (Table 2: Encounter 1). Pleconaril and high dose immune globulin did not improve his neurologic symptoms and he continued on conventional immune globulin therapy. His clinical and neurologic status declined over the next three years. Autoimmune liver disease with portal hypertension and hepato-splenomegaly led to an upper GI bleed at 28 years. He continued to suffer neurologic decline (Fig 1F) and died of CMV pneumonia with disseminated infection at 30 years.

P5 was born to unrelated parents. He presented at 2 years of age with recurrent perirectal abscesses, neutropenia, normal serum IgG and elevated IgM (Table 1). He was presumed to

have an (unknown) PID and remained healthy for the next 7 years on immune globulin. At 9 years, he suffered CNS *T. gondii* after briefly discontinuing immune globulin, but recovered with therapy and was placed on *T. gondii* prophylaxis and restarted on immune globulin. He was first diagnosed with CD40 ligand deficiency during this episode and remained free of overt active infection for the next 6 years. At 15 years, he had reactivation of CNS *T. gondii* with mild neurologic defects. He was treated for active disease and was discharged on immune globulin and *T. gondii* prophylaxis. At 18 years, he had an isolated seizure without evidence of infection. At 20 years, he had reactivation of CNS *T. gondii* secondary to nonadherence with prophylactic medications. He recovered with antimicrobials and high dose immune globulin but had new deficits. At 21 years, he was diagnosed with an extensive hepatic neuroendocrine tumor of suspected pancreatic primary for which, he underwent percutaneous hepatic perfusion. Two months later, he had progression of neurologic deficits but studies were non-diagnostic (Table 2: Encounter 1). He was administered high dose immune globulin and was discharged to follow up for systemic chemotherapy. His neurologic decline continued over the following month; he became only minimally ambulatory but CSF remained negative (Table 2: Follow up). His tumor progressed on systemic chemotherapy and he died one month later.

Autopsy

P4—Brain autopsy demonstrated severe chronic gray matter encephalitis of the neocortex, brainstem and deep structures with neocortical neuronal and pyramidal cell loss, perivascular (monocyte) cuffing, hippocampal gliosis and severe cerebellar degeneration with Purkinje cell and Dentate neuron loss (polioencephalitis type pattern). No viral or CMV inclusions or cytomegalic cells were identified in any brain region. The optic tracts and chiasm were thin and there was also patchy diffuse meningeal fibrosis. CMV PCR and studies for prion proteins were negative. Whole body autopsy demonstrated systemic adenopathy consistent with disseminated CMV infection. The enlarged mesenteric and cervical lymph nodes had normal morphology but sinus histiocytes demonstrated hemophagocytosis on CD68 staining. The bone marrow was normocellular with trilineage maturation and evidence of hemophagocytosis. Overall, he had increased activation and proliferation of benign macrophages with hemophagocytosis throughout the reticuloendothelial system consistent with hemophagocytosis syndrome. There was also portal vein fibrosis without evidence of cirrhosis consistent with non-cirrhotic (idiopathic) portal hypertension with consequent splenomegaly and esophageal varices.

P5—Autopsy demonstrated cystic brain lesions, parenchymal rarefaction, macrophages, axon/myelin loss and gliosis in the cortex, corpus callosum and cerebellum consistent with treated chronic toxoplasmosis. The tumor was composed of small to medium sized cells with irregular dark shaped nuclei with a high nuclear to cytoplasmic chromatin ratio, and larger bizarre multinucleated cells with numerous mitotic figures. There was tumor infiltration into the liver, duodenum and pancreas. This was consistent with an aggressive poorly differentiated pancreatic neuroendocrine tumor.

Clinical and Treatment Summary

The five patients detailed here are those who suffered neurologic decline out of a cohort of 31 patients with CD40L deficiency seen at the NIH. The median follow up for these five patients, from onset of neurologic symptoms to last contact, was 72 months (range: 3–144), and their median age at symptom onset was 9 years (range: 1–18). The median follow up for the remaining 26 with CD40L deficiency but without neurologic abnormalities was 70 months (range: 1–95), and their median age upon last clinical contact was 15 years (range: 1–33). One of the five patients with neurologic decline (#3) had received all age-appropriate vaccines including oral polio. The remaining four patients with neurologic decline had

uncertain immunization histories but two had received oral polio vaccinations (#2, #4). CSF pathogen evaluation for all patients is presented in the supplemental table.

All five patients detailed in this report received intravenous immune globulin after diagnosis of CD40L deficiency, titrated to maintain a serum IgG trough within the age appropriate normal range and/or to clinical effect [13]. Immune globulin was discontinued in one patient for two months secondary to concern of a possible anaphylactic reaction (#5) (Table 1). He was restarted on immune globulin soon after suffering an infection and remained on therapy until he died at 21 years. The typical dose/frequency of intravenous immune globulin was 300–500 mg/kg every 3–4 weeks; some patients received high dose immune globulin during presumed or proven acute infectious episodes. Two patients (#2, #4) received compassionate release pleconaril therapy [12], for presumed CNS enterovirus infection (2.4 mg, thrice daily for 10 days).

Discussion

Progressive neurodegeneration in the setting of primary immune deficiencies has been most notably demonstrated in X-linked agammaglobulinemia [14]. Patients with X-linked agammaglobulinemia are susceptible to chronic enteroviral meningo-encephalitis resulting in progressive neurologic decline which may be associated with other consequences of disseminated enterovirus infection [14,15]. The experience with X-linked agammaglobulinemia emphasizes the importance of B-cell responses in enteroviral CNS infection. Similarly, patients with CD40 ligand deficiency have impaired humoral responses and require lifelong immune globulin therapy [16]. Although CNS infections are well reported in CD40L deficiency, neurodegeneration is not [4,6]. The incidence of CNS infection in CD40L deficiency is approximately 13% (similar to the 12% incidence in X-linked agammaglobulinemia) [4,6,17]. Cumulatively, 29 cases of CNS infection due to enteroviruses (n=9), *T. gondii* (n=3), *S. pneumoniae* (n=1), JC virus (n=4), CMV (n=2), *Mycobacterium bovis* (n=1), *Cryptococcus neoformans* (n=2), and unknown/aseptic (n=7) [4–8] have been reported. While the heterogeneous nature of these studies precludes uniform conclusions, up to 45% of affected patients died or had neurologic sequelae [4–8].

In this report, we present five patients who suffered severe neurologic disease with a high mortality rate (60%). Imaging was remarkable for severe CNS atrophy, EEG indicated diffuse cerebral dysfunction, and most patients had a documented decline in cognitive function coincident with symptom onset (mean IQ $\pm$ SD: 68 $\pm$ 13). Despite multiple evaluations, including at initial presentations and during periods of ongoing decline, pathogens were identified in only one patient (#5). The most clinically salient feature of our cohort is therefore that four patients (#1–4) suffered marked neurologic decline with a chronic enteroviral meningo-encephalitis-like phenotype in the absence of identifiable pathogens.

No patient had clinical or laboratory evidence of disseminated viral infection (e.g. arthritis, viral pneumonia, viremia) concurrent with the neurologic decline. One patient (#4) succumbed to disseminated CMV infection and hemophagocytosis syndrome. However, there was no evidence of active CMV meningo-encephalitis either on imaging or at autopsy. Moreover, his neurologic decline began years prior to the CMV infection. Many of our patients had pulmonary complications of severe recurrent sinopulmonary infections and two had multi-system dysfunction as consequence of autoimmune hepatitis (#4) and tumor (#5). However, these systemic complications are unlikely to be related to the neurologic decline as these patients were not oxygen dependent (retained pulmonary reserve), and had no laboratory evidence of hepatic dysfunction. While the cachexia was the ultimate cause of

death in patient #5, his neurologic decline preceded the tumor and there was no evidence of CNS tumor metastasis at autopsy.

The seasonal (summer) appearance of symptoms coupled with the prodrome preceding the neurologic decline and varying degrees of CSF pleiocytosis (in 3/4 patients evaluated) are consistent with an infectious encephalitis. The virus was furthermore presumed to be an enterovirus because of the susceptibility of patients with humoral defects to enteroviral CNS infections [14,18–20], the demonstrable B cell defects in CD40 ligand deficiency, and because enteroviruses are the most commonly isolated pathogens in encephalitis/meningitis in patients with CD40 ligand deficiency in whom a pathogen is identified [4,6]. Enteroviruses are also a common cause of infectious meningo-encephalitis in immune competent patients.

Four patients (#1–4) were on standard intravenous immune globulin therapy [13] at the time of symptom onset. While immune globulin therapy has reduced the incidence and severity of CNS enterovirus infection in patients with defective humoral immunity, it apparently does not provide immunity to these infections in all cases. Several patients with humoral and combined defects have developed chronic enteroviral meningoencephalitis [5,14,18,20], or had disease relapse [14,21,22] on conventional immune globulin therapy. This suggests that serum IgG supplementation may not be sufficient for immunity to some CNS viral infections, at least in some patients. Alternatively, some IgG preparations may lack adequate titers of neutralizing antibodies to specific viruses [14,19,21–23], or intravenous immune globulin therapy may not provide protective levels of IgG in the CSF. In these respects, intraventricular IgG or intravenous immune globulin titrated to maintain serum trough above 800 mg/dl has been variably successful in chronic enteroviral meningo-encephalitis [16,19,21,22].

Although an infectious etiology for the neurologic decline is the most plausible explanation in our patients, the absence of proof necessitates the consideration of other etiologies. Pathogens were not identified in four patients (#1–4). Three of these patients were evaluated for pathogens, including enteroviruses from multiple sites (CSF, stool, nasopharyngeal swabs and colonic biopsies) at multiple times. Despite this intensive search, studies including PCR and tissue culture for viruses, were negative in all four (Table 2). Identification of viruses has variable sensitivity depending on the virus and the timing of evaluation relative to the disease course. In general, PCR is highly sensitive early in infection, but loses sensitivity during convalescence (REF). The high sensitivity of PCR for enterovirus suggests that our patients were likely to test positive at some time in their disease course if they were etiologic (REF). The reason for the negative results (for multiple pathogens) is unclear. It is possible that our PCR probes were not specific for the etiologic enterovirus serotypes in our patients or they had infections caused by non-cultivated organisms or unknown pathogens. Notably, pathogens were not identified in 24% (7/29) of the reported cases of CNS infection in CD40 ligand deficiency [4–6,8]. Reactivation of polio is another possibility in the three patients who received (oral) inactivated polio vaccinations. Reactivation of live attenuated viruses has been reported in patients with immune deficiencies. However, the timing of presentation, course and neurologic features make that unlikely. Immune globulin therapy itself has been associated with neurodegeneration, but whether it is causative remains to be determined [24].

The neurologic decline in patient 5 was coincident with chronic CNS *T. gondii* infection, and may have been due to that alone. Host resistance to *T. gondii* depends on the Th1 immune response characterized by the production of interleukin-12 (IL-12) by antigen presenting cells and gamma interferon (IFN- γ) by activated CD4⁺ T cells [25]. Compared with healthy controls seronegative for *T. gondii*, patients with XHIM syndrome produce

lower levels of IL-12 and INF- γ upon stimulation with *T. gondii* tachyzoites *in vitro*. Moreover, these deficits can be rescued *in vitro* by soluble CD40 ligand trimer, confirming that they are a direct result of CD40 ligand deficiency [25]. Consistent with our experience, defects in the CD40 ligand-dependent INF- γ /IL-12 axis are associated with severe CNS toxoplasmosis in murine models.

CD40L is necessary for humoral antiviral responses [26], but its role in cellular antiviral responses is uncertain. Animal models provide evidence for both CD40 ligand dependent and independent antiviral responses depending on the chronicity of infection [27], type of virus [28] and on whether CD40 ligand is required for cross priming of CD8+ T cells [29,30]. Patients with CD40L deficiency have impaired T-cell proliferation to antigens [31], but whether this contributes to susceptibility to viral CNS infection is uncertain. Many patients with T cell primary immune deficiencies are susceptible to viral infections [32–35], and some suffer severe neurodegeneration due to CNS enteroviral infections [36]. However, because these patients typically have profound combined immune defects, the specific contribution of CD40 ligand to antiviral responses is difficult to definitively ascertain.

As survival rates of patients with immune deficiencies improve with bone marrow transplantation and gene- and cytokine-based therapies, early detection and treatment of CNS complications may provide guidance for early intervention and reduce long term morbidity and neurologic sequelae. With microarray technology, chips that contain representative DNA sequence of nearly 1,000 viruses been used successfully to search for novel viruses in cases of respiratory infections, meningitis, as well as cases of severe encephalitis and hepatitis [37–40]. Such refined genomics approaches are currently being employed to delineate the etiology of neurodegeneration in CD40 ligand deficiency and could also be helpful in the diagnosis of viral infections in related inherited immune deficiency disorders.

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Figures 1A and 1B

Figures 1C and 1D

Figure 1E and 1F

Figure 1. Radiographic findings of patients with CD40 ligand deficiency and neurodegeneration (A) T1 weighted brain MRI obtained upon presentation in patient 1 and (B) three months later demonstrating progressive cortical atrophy. TR/TE: 400/10 ms, field of view: 20–22 cm, matrix: 256×192 , 1 excitation, 5 mm slice thickness. (C) Fluid inversion recovery attenuation weighted MRI obtained in patient 2 at presentation. (D) Patient 2 three years later (one month after completing pleconaril therapy) demonstrating progressive atrophy and periventricular encephalomalacia (arrows). TR/TE: 10,000/145 ms, field of view: 20–22 cm, matrix: 256×192 , 1 excitation, 5 mm slice thickness. (E) T1 weighted MRI obtained in patient 4 when 6 years after presenting with neurologic decline and then (F) 4 years later demonstrating progressive atrophy (interval gyral thinning/sulcal widening (arrows)). TR/TE: 400/10 ms, field of view: 20–22 cm, matrix: 256×192 , 1 excitation, 5 mm slice thickness.

Table 1

Clinical Summary

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age of XHIM syndrome diagnosis	12 months	8 months	14 months	2 years	9 years
Presenting infections and medical history	-failure to thrive -recurrent bacterial sinusitis -recurrent <i>Candida albicans</i> otitis	- <i>Pneumocystis (carinii) jirovecii</i> pneumonia -recurrent <i>Candida albicans</i> otitis	-ulcerative epiglottitis (bacterial) -neutropenia - low IgG and IgA with elevated IgM	-recurrent bacterial sinusitis, otitis and pneumonias -viral meningitis at 6 months of age -perirectal abscess -neutropenia 2–18 years -recurrent URIs -recurrent <i>S. pneumoniae</i> pneumonias	by 2 years -recurrent bacterial sinusitis and otitis -oral thrush -neutropenia -normal IgG and IgA, elevated IgM
Age of CNS symptom onset	11 years	6 years	14 months	18 years	9 years
Presenting neurologic signs/findings	1 month prodrome attributed to viral URI -no overt CNS signs <i>Neurologic findings^a</i> : -photophobia -headaches -hypersomnolence	1 month prodrome attributed to viral URI -no overt CNS signs <i>Neurologic findings^b</i> : -dysarthria -dysmetria -impaired fine finger coordination -fine choreoathetotic	14 months: -hypersomnolence mild impairments in: -gross motor development -gait/mobility -receptive/expressive language 15 months: -tonic-clonic seizure	<i>Neurologic findings^c</i> : -visual decline -cognitive decline resulting in cessation of college -psychomotor slowing -mild ataxia -mild hypertonia -mild hyperreflexia -mild tremor	9 years: -headache -photophobia -mental status changes - <i>T. gondii</i> on brain biopsy -elevated ICP requiring ventriculostomy

Age of XHIM syndrome diagnosis	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
	12 months	8 months	14 months	2 years	9 years
	- vertigo -dysarthria -hemiparesis -hypertonia -ataxia	movements -hypotonia -ataxia			15 years: -reactivation of CNS <i>T. gondii</i> -mild ataxia -cognitive decline
Ophthalmologic exam	Optic pallor, 20/400 (bilaterally)	Optic pallor (bilaterally)	-	Optic pallor (bilaterally), 20/200 (right), 10/25 (left)	
Interval of neurologic follow-up	3 months	3–6 years	1 month	3–10 years	2–3 years
Progressive neurologic signs/findings	-dementia -progressive dysarthria -total vision loss (optic neuropathy) -progressive ataxia (non-ambulatory) -inability to complete ADLs	9 years: -severe progressive dysarthria (could only say 'yes' or 'no') -spasticity -progressive ataxia -inability to complete ADLs	-ataxia -mild hypotonia	24 years: -progressive cognitive/memory deficits -progressive dysarthria -choreoathetosis -progressive ataxia -inability to complete ADLs	18 years: -tonic-clonic seizure 20 years: -right face/arm numbness -hyperreflexia and spasticity in the right upper and bilateral lower extremities -ataxia 21 years: -acute dysarthria -acute left sided

Age of XHIM syndrome diagnosis	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
	12 months	8 months	14 months	2 years	9 years
	muscle control -progressive ataxia (non-ambulatory) -inability to complete ADLs weakness -progressive spasticity -progressive ataxia				
IQ	69	50	Developmental regression	77	77
Disposition Cause of death	Died age 12	Died age 11	Alive	Died age 30	Died age 21 Neuroendocrine tumor

Abbreviations:

IQ: intelligence quotient

ADLs: activities of daily living

URI: upper respiratory tract infection

a: Symptoms progressively developed over 2 months

b: Symptoms progressively developed over 1.5 months

c: Symptoms progressively developed over 3+ months

a, b, c: neurologic symptoms not preceded by, or associated with, constitutional or overt CNS signs

Table 2

Diagnostic Evaluation

Serum	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	Encounter 1	Follow up	Encounter 1	Follow up	Encounter 1	Follow up	Encounter 1	Follow up	Encounter 1	Follow up
IgG (mg/dl)	1280	5070	-	502	720	823	-	727	-	727
IgA (mg/dl)	<10	<10	-	<10	<7	<10	-	15	-	15
IgM (mg/dl)	160	146	-	97	96	381	-	27	-	27
Glucose (mg/dl)	104	121	-	93	139	78	129	104	-	104
WBC (1000/ μ l)	9	7	7	6.65	25	1.26	1.88	3.11	-	3.11
CSF										
WBC (#/mm ³)	2	29 ^a	1	3	106	10	3	3	-	3
Protein (mg/dl)	64	29	26	24	38	46	36	40	-	40
Glucose (mg/dl)	54	61	55	52	64	44	52	51	-	51
CSF evaluation for pathogens										
Enterovirus	Negative	Negative	-	Negative	-	Negative	-	Negative	-	Negative
CMV	Negative	Negative	-	Negative	-	-	-	Negative	-	Negative
VZV	Negative	Negative	-	Negative	-	-	-	Negative	-	Negative
HSV	Negative	Negative	-	Negative	-	-	-	Negative	-	Negative
EBV	Negative	Negative	-	Negative	-	-	-	Negative	-	Negative
JC virus	-	-	-	-	-	-	-	-	-	-
Influenza A and B	-	-	-	Negative	-	-	-	-	-	-
<i>Cryptococcus neoformans</i> antigen	Negative	-	Negative	Negative	-	-	-	-	-	-
Fungi	Negative	-	-	Negative	-	-	-	Negative	-	Negative
AFB	Negative	-	-	-	-	-	-	Negative	-	-
<i>Borrelia burgdorferi</i>	-	Negative	-	-	-	-	-	-	-	-
Gram stain/culture	Negative	-	Negative	Negative	Negative	-	-	Negative	-	Negative
<i>T. gondii</i>	-	-	-	-	-	-	-	-	-	-
EEG										
	-	-	Normal	Diffuse slowing	Diffuse slowing	Diffuse slowing	Diffuse slowing	Diffuse slowing	Diffuse slowing	Focal cortical hypexcitability

Serum	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	Encounter 1	Follow up	Encounter 1	Follow up	Encounter 1	Follow up	Encounter 1	Follow up	Encounter 1	Follow up
MRI and diagnostic studies	Mild global atrophy and mild (bilateral) optic nerve atrophy	Progressive global and bilateral optic nerve atrophy	MRI: Normal EMG: Normal	Global atrophy, parieto-occipital demyelination	Cerebral atrophy		Severe global atrophy, mild atrophy of the optic nerves (bilaterally) and corpus callosum		Cerebral atrophy	Progressive cerebral atrophy

Normal range:

Serum:

IgG: 642–1730 mg/dl

IgA: 91–499 mg/dl

IgM: 34–342 mg/dl

WBC: 3.3–9.6 1000/ μ l

CSF:

WBC: 0–5 mm³

Glucose: 50–70 mg/dl

a: 92% lymphocytes (normal: 40–80%), 1% Neutrophils (normal 0–6%)

Abbreviations:

AFB: Acid fast bacillus

HSV: Herpes simplex virus-1

MRI: Magnetic resonance imaging

VZV: Varicella zoster virus

CMV: Cytomegalovirus

EEG: Electroencephalography

WBC: White blood cells

EBV: Epstein-Barr virus

CSF: Cerebral spinal fluid

JCV: JC virus

EMG: Electromyography