Common Variable Immunodeficiency and Its Inflammatory Neurological Manifestations: A Case Report and Literature Review

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Abstract

Purpose

Common variable immunodeficiency disorders (CVID) are a group of primary immunodeficiencies characterized by impaired immunoglobulin production and dysregulated immune response. Neurological manifestations have been described in few patients, and little is known about its clinic and therapeutic approach. Thus, the aim of this work was to review the literature on it and to help differentiate CVID from its mimics, especially sarcoidosis.

Methods

We described a case report and included a literature review of inflammatory neurological involvement in CVID.

Results

A 32-year-old female patient with a medical history of recurrent bacterial infections, temporal focal epilepsy and granulomatous lung disease under study, and cervix squamous cell carcinoma, was initially admitted to the emergency department due to intracranial hypertension. After excluding infectious and neoplastic etiologies, the most likely hypothesis was that granulomatous pulmonary, cerebral, and leptomeningeal inflammatory involvement were associated with sarcoidosis. Two years later, a diagnosis of CVID was made, and the patient was secondarily diagnosed with Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD) and related inflammatory brain disease – both complications of CVID. After starting targeted treatment with immunoglobulin replacement and pulse glucocorticoids followed by a chronic taper, the patient became stable. However, three consecutive failures in immunoglobulin intake led to disease recurrence with relapse of neurological manifestations.

Conclusion

This case illustrates the complex multiple organ manifestations of CVID. When granulomatous conditions arise in these patients, GLILD with multisystem involvement should be taken in consideration. Early treatment with combined steroids and immunotherapy seems to be effective in controlling CVID's neurological manifestations.

Introduction

Common variable immunodeficiency disorders (CVID) are the most clinically significant primary immunodeficiency in adults, accounting for 90% of symptomatic primary antibody deficiencies [1]. They are characterized by low levels of serum immunoglobulin (Ig) G with IgA and/or IgM deficit due to a primary antibody failure [2]. Current estimates suggest a prevalence ranging from 1:25,000 to 1:100,000 in Caucasian individuals [1, 3]; recently, a Finnish study suggested a higher prevalence of 6.9:100,000 [3]. By definition, the causes of CVID are unknown, but an increasing number of monogenic causes and a digenic disorder have been described in patients with a CVID phenotype. Indeed, a causative variant, for example in NFKB1, NFKB2, CTLA-4, TCF3 genes, has been identified in approximately 25% of the cases in non-consanguineous populations [1]. Although commonly associated with recurrent bacterial infections, other systemic conditions such as autoimmune manifestations, inflammatory disorders and malignancy have been described [4]. Approximately 20% of these patients develop at least one autoimmune disease, frequently autoimmune thrombocytopenia, autoimmune hemolytic anemia, pernicious anemia, and rheumatoid arthritis [1]. Neurologic dysfunction in CVID is less known but can be associated with significant morbidity and mortality [5]. Thus, starting from a challenging clinical case, the aim of this work was to review the literature on the neurological manifestations of CVID and to help differentiate CVID from its mimics, especially sarcoidosis.

Methods

We present a CVID patient with significant neurologic morbidity and report an extensive literature review on inflammatory neurological involvement in this disease. Articles written in English, searched in PUBMED and academic google, using the Key Words “common variable immunodeficiency”, “granulomatous disease” and “neurological manifestations” were included. We extracted data from case series, observational studies, systematic or no systematic reviews, and case reports.

Results

A 32-year-old Caucasian woman was admitted to the emergency department in April 2015 due to a holocranial headache with 2 weeks evolution of increasing intensity until 9/10 in numerical pain scale, worsened by lying down. Additionally, vomiting, fever, and gait imbalance were reported. She had a past medical history of recurrent respiratory bacterial infections requiring antibiotics, adult-onset (30 years old) temporal focal epilepsy of unknown etiology (initially medicated with sodium valproate 1000 mg/day, which was suspended in 2016, and later levetiracetam 1000 mg/day, suspended in 2020), granulomatous lung disease under study since 2013 at another institution (suspected sarcoidosis), and squamous cell carcinoma in situ of the uterine cervix. She had a family history of early onset neoplasms (gastrointestinal, breast, and ovary); with no consanguinity. On admission, she presented papilledema and right hemiataxia. A contrast brain CT showed at least two enhancing lesions in the right cerebellar hemisphere with a possible dural involvement, with marked perilesional edema, obstructive hydrocephalus, and brainstem compression (figure 1). The clinical picture was compatible with intracranial hypertension. Dexamethasone 5mg was urgently started, with symptom improvement, and the patient was admitted to an intensive care unit. The serological study showed

low total protein levels (55.0 g/L, normal range, NR, of 64-83 g/L) and low serum IgG (409 mg/dL, NR=520–1.560 mg/dL). Full blood count, erythrocyte sedimentation rate, vitamin B12 levels, thyroid function, autoimmune study [including rheumatoid factor, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), anti-double strand DNA antibodies (anti-dsDNA), anti-Ro (SS-A), and anti-La (SS-B), anti-cardiolipin, anti-ovarian, and anti-neuronal antibodies], serum angiotensin-converting-enzyme (ACE) and tumor markers [carcinoembryonic antigen, carbohydrate antigen (Ca) 19-9, Ca 125] were normal/negative. Antibodies against myelin-oligodendrocyte-glycoprotein (Anti-MOG) and aquaporin 4 (Anti-AQ4) were not detected. Serum polymerase chain reaction (PCR) for varicella-zoster (VZV) and herpes simplex (HSV) 1 and 2, *Treponema pallidum* particle agglutination (TPPA), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), *Toxoplasma gondii*, and *Borrelia burgdorferi*'s serology were negative. CSF analysis showed mild pleocytosis (6 cells/ μ l) with lymphocyte prevalence (99%), normal proteins (0.29 mg/L; NR=0.18-0.45 mg/L), no glucose consumption, and normal ACE. CSF cytology was negative for malignancy; CSF bacterial, viral, and fungal workup was also negative. Brain MRI (April 28) revealed signs of cortico-pial infiltration at the level of both cerebellar hemispheres and right inferior temporal region, associated with edema, leading to left fourth ventricle compression and enlargement of the supratentorial ventricular system, with incipient signs of CSF transudation (figure 1, panel B) – suggesting an inflammatory process of granulomatous and/or infectious etiology, not excluding secondary neoplasia. Thoracic-abdominopelvic CT showed architectural distortion of the lung parenchyma, interlobular septal thickening, and linear and nodular densifications, mainly at the subpleural level and at the basal lung, with cylindrical bronchiectasis and several bilateral micronodules; normal spleen size in the upper limit of normality. Bronchoscopy revealed a normal total and differential cell count, absence of malignant cells, and negative microbiological study in bronchoalveolar lavage. A CT-guided lung biopsy showed lung parenchyma extensively occupied by small lymphoid cell infiltrates and areas of granulomatous outline, with rare giant cells without necrosis. The test for acid-resistant bacilli was negative. Pulmonary function tests were normal. Upper and lower gastrointestinal endoscopy, and cervical and breast ultrasound displayed no alterations. During hospitalization, she continued dexamethasone 4mg three times/day with progressive symptom improvement. She remained afebrile since admission. Ten days after starting glucocorticoid therapy (May 7), a second brain MRI found a clear reduction in the corticopial enhancement areas in the right cerebellar hemisphere, and no enhancement in the remaining areas, with a resolution of ventricular dilatation (figure 1, panel C). The patient was discharged with the diagnosis of sarcoidosis with pulmonary and neurological involvement, with tapering steroid therapy (initially 1mg/Kg/day, tapering within 4-6 weeks to 20mg/day). Her symptoms and brain MRI abnormalities resolved within 3 months.

After this neurological presentation, CVID and granulomatous lung disease secondary to immunodeficiency (Granulomatous and Lymphocytic Interstitial Lung Disease - GLILD) diagnosis was made. Diagnostic work-up showed a low level of total IgG (380 mg/dL, NR<650 mg/dL), IgA (30 mg/dL, NR=47-206 mg/dL), IgM (47mg/dL) and IgE (<2 kU/L), as well as lymphopenia, defective response to pneumonia vaccine (Pneumovax® 23) antigens, decreased switched memory B cells (7.9% of IgD-CD27+ B cells) and increased CD21low B cells (21.3%). Cellular immune response was also affected, with inversion of the (CD3⁺)CD4⁺/CD8⁺ ratio, low naïve CD4+ T cells (24% CD4+CD45RA+ cells) and increased CD4+ memory T cells (72% CD4+CD45+RO+ cells). The patient was started on IgIV 400mg/kg every three weeks (added to low-dose oral steroid therapy – at that moment with 10mg/day of prednisolone).

She remained in clinical and imaging remission until June/2020 (figure 2), when, after missing three doses of IVIg during the COVID-19 pandemic, she complained of cervicgia with occipital irradiation, refractory to analgesia. Brain CT showed a new hypodensity on the left cerebellar hemisphere, with a slight mass effect (figure 2), which motivated hospitalization. Cervical CT did not show any lesion. A new MRI confirmed cortico-pial enhancement in the cerebellar hemispheres and bilateral pons, and pachymeningeal enhancement in the cerebellar tent, with no restriction to diffusion (figure 2). MRI-spectroscopy did not suggest a malignant lesion. New CSF analysis revealed pleocytosis (112 cells/ μ l), with lymphocyte prevalence (99%), and mildly elevated protein level (0.78 mg/L), glucose consumption (70% of the serum value), normal ACE and Adenosine deaminase test (ADA), and negative bacteriological and mycobacteriological study. Oligoclonal bands were positive in CSF and negative in serum. Given the higher risk of CVID patients to develop lymphoproliferative diseases, cytological and imagiologic examinations were carried out to exclude CNS lymphoma. No malignant cells were detected in the CSF. A full-body 18-FDG Positron Emission Tomography (PET)/CT study revealed irregular densifications in both lungs (nodular and ground glass) and mediastinal-hilar bilateral adenopathies, with increased FDG-F18 uptake, and heterogeneous distribution of cerebellar FDG-F18 (figure 2). Based on these findings, a relapse of inflammatory brain disease associated with CVID was assumed. The patient underwent a cycle of high-dose steroid therapy (methylprednisolone 1 g for 5 days), followed by a maintenance dose of oral prednisolone 40 mg/day, associated with trimethoprim-sulfamethoxazole three times/week and IVIg replacement therapy, as described above.

After 3 months, the patient was in clinical and imaging remission from a neurological point of view, with stability of the pulmonary radiographic findings (no respiratory symptoms). Currently, she keeps surveillance in neurology consultation every 3 months. The last clinical evaluation was on October/2021; she was asymptomatic, and the last brain MRI assessment in December/2021 showed no alterations.

Discussion

We report an uncommon and underreported manifestation of CVID: an inflammatory brain lesion in a patient with a lung granulomatous disease (GLILD).

According to the European Society for Immunodeficiencies (ESID), CVID patients are characterized by a family history of antibody deficiency and/or personal history of increased susceptibility to infection as well as autoimmune, granulomatous, or/and lymphoproliferative diseases [6, 7]. These clinical features combined with a marked decrease in IgG and IgA (with or without low IgM levels), and evidence B cell differentiation impairment allow the diagnosis of this disorder [1, 7]. Being a diagnosis of exclusion, transient and secondary causes of hypogammaglobulinemia, such as drugs (particularly rituximab and anticonvulsants) and profound T-cell deficiency should be first considered [1, 7]. In the present case, considering the clinical, imaging and disease progression, drug-related immunodeficiency was unlikely.

Although the most relevant cellular implication in CVID is related to B lymphocytes, it has been increasingly demonstrated that T cell impairment is a frequent and important finding in these patients. Our patient fulfills ESID diagnostic criteria for CVID, with additional evidence of decreased switched memory B cells, increased CD21low cell numbers, and T cell population alterations (decreased naïve CD4+ T cell numbers as well as implications in the CD4⁺/CD8⁺ ratio).

These findings are usually associated with the severity and poor outcome of CVID. Recent evidence indicates that lymphoproliferation and granulomatous diseases are mainly observed in patients with severe depletion of switched memory B cells and CD4+ naïve T cells (8). This subgroup of CVID patients is also characterized by an increased frequency of splenomegaly and malignancies [8].

Our patient had a diagnosis of a non-infectious inflammatory brain lesion secondary to CVID. Among the described cases in the literature (Table 1), infections are the main cause of CVID-associated neurological dysfunction, particularly meningitis and encephalitis [4, 9]. Autoimmune/inflammatory conditions comprise the second largest category of neurologic complications (1.4% of CVID patients) [4, 5], including myelitis [5, 9–12], brain inflammatory/demyelinating disease [4, 5, 7, 13], unilateral [2, 5] and bilateral [14] optic neuritis, cerebral vasculitis [5], and encephalopathy (autoimmune encephalitis [5] and acute encephalomyelitis [15]). Van de Ven et al. [16] reported a 4% prevalence of inflammatory CNS disease, higher than previously reported. Of the studies reporting inflammatory lesions, the majority are case reports [2, 4, 7, 9–15]; there are few observational studies [5, 16–18]. Although some of these studies report a higher frequency of neurological CVID manifestations in females [9, 17], in others [16], age and gender distribution were comparable between CVID controls without CNS manifestations and CNS disease patients (mean age 46.6y ±15 in controls vs. 44.1y ±11.0 in CNS disease). Overall, some authors suggested that CNS involvement in CVID is not an isolated manifestation but rather a symptom of severe systemic immune dysregulation, possibly due to failure of peripheral tolerance [2].

Table 1
Non-infectious inflammatory neurological manifestations of CVID

Author, year	Type of study	Gender, age, clinical history	CVID diagnosis	Neurological manifestation	Complementary study	Other CVID manifestations	Treatment and prognosis
Kumar et al., 2008 [11]	Case-report	Female, 64y Recurrent infections and idiopathic thrombocytopenic purpura, vitiligo, psoriasis and diabetes	Yes	Myelitis	CSF: normal MRI spine: cervical and thoracic cord hyperintensity with contrast enhancement MRI Brain: contrast enhancement in the right basal forebrain	Pulmonary sarcoidosis suspected	Pulse glucoc followed by taper+Infliximab Improvement findings, Persistent neurological symptoms
Sempere et al., 2011 [14]	Case-report	Male, 26y Hemolytic anemia, autoimmune thrombocytopenia and neutropenia	Yes	Bilateral optic neuropathy	CSF: normal MRI Brain: mild enhancement of both optic nerves without other abnormalities		Methylprednisolone IV and taper + prednisone + (0.4 g/kg 3-3 months) Asymptomatic
Danieli et al., 2012 [12]	Case-report	Female, 71y	Yes	Acute myelitis	MRI spine: cervical and thoracic cord hyperintensity with contrast enhancement - C3–C4 and T5–T10 segments, mainly in posterior columns MRI Brain: normal		Pulse glucoc without chronic glucocorticoids Intramuscular No new lesions MRI after treatment Persistent neurological symptom
Jabbari et al., 2014 [10]	Case-report	Female, 41y Recurrent Diffuse adenopathy, pyogenic infections and idiopathic thrombocytopenic purpura	Yes	Longitudinally extensive myelitis	CSF: acellular, 0.56 g/L protein, negative oligoclonal bands MRI spine: longitudinally extensive cord signal T2 and contrast enhancement in conus medullaris MRI Brain: normal		Pulse glucoc without taper glucocorticoids IVIg + Inpatient rehabilitation Improvement findings Resolution of neurological symptoms
Nguyen et al., 2016 [4]	Case-report	Female, 40y Lymphocytic colitis	Yes, 2007	2009: unilateral optic neuritis and multifocal choroidopathy 2013: episodic visual distortion and headache 2014: seizure	CSF 2013: lymphocytic pleocytosis, mildly elevated protein, and positive BOCs Brain MRI: 2 enhancing lesions with mild mass effect in the cerebellum, leptomeningeal enhancement Brain biopsy (2x): modest astrogliosis, no granulomas	2007: Lymphocytic interstitial pneumonia (LIP)	Pulse glucoc without a taper rituximab + IV Since the admission rituximab – no neurological with near-complete resolution of symptoms and findings
Abati et al., 2018 [2]	Case-report	Male, 26y	Yes	Optic neuropathy	CSF: marked pleocytosis (200 cells/ul), mildly elevated protein level (56 mg/dl) Brain MRI: Enlargement and hyperintensity of the optic nerve in fat-suppression		Course of IV methylprednisolone (1 g/d for 5 days and taper prednisone) Remained asymptomatic follow-up

Author, year	Type of study	Gender, age, clinical history	CVID diagnosis	Neurological manifestation	Complementary study	Other CVID manifestations	Treatment and prognosis
Najem et al., 2018 [17]	Observational and retrospective study	N=19	8 of the 13 patients were diagnosed with CVID after the diagnoses of CNS granulomas	68.4% (n=13) granulomas ≥2 organs including CNS, 31.6% (6/19) CNS granulomas only	CSF (n=5): Increased total proteins with/without lymphocytic pleocytosis in 80% High serum ACE in 42.8% (3/7) MRI: brain mass (70%), leptomeningeal enhancement (10%), non-specific white matter lesions (10%) and absence of normal signal of neurohypophysis (10%)		26% (5/19) steroids only, 26.3% (1/4) steroids alone immunoglobulin only, 15.8% (1/6) infliximab, 15.8% (1/6) other (methotrexate, cyclosporine, azathioprine, cyclophosphamide, 10.5% (2/19) rituximab, and (1/19) refused therapy
Farshad et al., 2019 [9]	Case-report	Female, 30y Recurrent upper respiratory infections, vitiligo, and immune thrombocytopenic purpura	Yes	Transverse myelitis	Spinal MRI: signal hyperintensity. Brain MRI: hyperintensity in the right middle frontal gyrus		Chronic glucocorticoids without pulse Methotrexate Improvement findings Persistent neurological symptoms in
Galli et al., 2019 [19]	Case series (University of Utah Healthcare system with CVID and co-existing epilepsy)	N=5 (3 male, 2 female) Mean Age Seizure Onset: 29y (6.4) Mean Age CVID Diagnosis: 37y (22.8)	Yes	All patients had atypical seizure: behavioral arrest, consciousness alterations, and/or amnesic episodes. Generalized tonic clonic seizures less common.	Most had abnormal imaging findings, most commonly temporal lobe asymmetry.		Most had improvement with antiepileptic therapy. IVIg improve epileptic symptoms.
Cowen et al., 2020 [7]	Case-report	Female, 50y Evans syndrome	8y after neurological manifestations	Cerebellar ataxia First diagnosis: neurosarcoidosis	Normal CSF Brain MRI: signal intensity lesion in right cerebellar hemisphere with mass effect Brain biopsy: focal infiltration with macrophages and lymphocytes (mainly T-cells); no granulomas	GLILD: 10y after neurological manifestation (60y)	Corticosteroids, methotrexate, immunoglobulin replacement (initially intravenously, subcutaneous) Clinical and in remission in

Author, year	Type of study	Gender, age, clinical history	CVID diagnosis	Neurological manifestation	Complementary study	Other CVID manifestations	Treatment and prognosis
Lee et al., 2020 [5]	Cross-sectional survey (US Immunodeficiency Network – registry of primary immunodeficiencies)	601 patients, 29.6 y (range 0–73), 65.9% female	Yes	<p>≥1 neurologic symptom in 49.1% (601/1224):</p> <ul style="list-style-type: none"> - Neuropsychiatric (53.7%) - Headache (35.6%) - Developmental delay (12.5%) - Neuropathy (10.8%) - Seizures (10.7%) - Endocrine disorder (6%) - Vertigo (5%) - Cerebrovascular disease (4.7%) - changes in sensory acuity/function (4.5%) - Sleep disorders (4.2%) - Movement disorders (3.7%) - Cognitive impairment (2.8%) - Ataxia (2.5%) - Altered mental status (0.5%) 	17 (1.4%) with neurologic autoimmune diagnoses: cerebral vasculitis (n=5) and demyelinating disease (n=5), brain granuloma (n=2), autoimmune sensorineural hearing loss, autoimmune encephalitis, leukoencephalopathy, myasthenia gravis, neuritis, neuromyelitis optica, and chronic lymphocytic inflammation		Corticosteroids (n=12), azathioprine (n=2), abatacept (n=1), hydroxychloroquine (n=1), methotrexate (n=1), mycophenolate mofetil (n=1), sirolimus (n=1)
Shribman et al., 2020 [15]	Case-report	Male, 31 y Afro-caribbean	As a teenager	<p>Headache: acute-onset, constant headache for 1 month without fever, meningism, seizures, nor any preceding illness after missing his treatment with IVIG</p> <p>Encephalomyelitis with retinopathy</p>	<p>CSF: 68 lymphocytes and 1.31 g/L protein</p> <p>CT brain: hyperdense lesion in right callosal body</p> <p>MRI: restricted diffusion and contrast-enhancement with several lesions around the lateral ventricles; diffuse intramedullary signal change within the entire spinal cord</p>		<p>Regular IVIg</p> <p>Symptoms and abnormalities resolved with steroids</p> <p>Retinal findings unchanged</p>
Van de Ven et al., 2020 [16]	Observational and retrospective study	N=17	Yes	Loss of sensory or motor function, headache, or epilepsy	Contrast-enhancing lesions in brain and spinal cord: the most common findings on MRI. Molecular defect in 8 patients, including mutations in CTLA4, NFKB1, and CECR1		CNS involvement usually responded well to high-dose steroids, but required maintenance therapy to prevent relapse
Strunz et al., 2021 [18]	Observational and retrospective study	N=50	Yes	-	-	12% (n=6) radiological and/or histological confirmed GLILD diagnosis	Synchronous CNS involvement. GLILD-patients responded to rituximab treatment. All patients showed radiological improvement and stabilization of pulmonary function.

CVID-associated neurological symptoms are considered rare; however, a recent study, including 601 patients selected from the United States Immunodeficiency Network, showed that at least one neurologic condition/symptom was reported in 49.1% of CVID patients – mostly neuropsychiatric symptoms (53.7%), followed by headache (35.6%) and developmental delay (12.5%) [5]. In another study, Najem et al. [17] reported that, among the CVID patients with granulomatous disease, 68.4% (13/19) had granulomas involving ≥ 2 organs, including the CNS, and 31.6% (6/19) had isolated CNS granulomas. In this study, the most frequent initial neurological symptom was seizures (31.6%), followed by de novo headache and/or worsening headache (21%) and vision loss (15.7%). In our patient, headache was the initially recognized and recurrent manifestation of inflammatory cerebral disease secondary to CVID. However, she had focal temporal epilepsy of undetermined etiology, with her first seizure at 30 years of age, that could be related to neurological manifestations of CVID. Galli et al. [19], in a case series of 5 patients, described an association between CVID and autoimmune-mediated epilepsy and/or atypical epilepsy, including behavioral arrest, alterations in consciousness, and/or amnesic episodes, and less commonly generalized tonic-clonic seizures. A majority of these patients had abnormal imaging findings, most commonly temporal lobe asymmetry, and most improved with antiepileptic therapy, but not with IVIG [19].

Based on Van de Ven's [16] diagnostic and treatment algorithm, we proposed an approach to patients with suspected CVID when neurological manifestations (Table 2). According to Van de Ven's [16] and Farshad et al. [9] the first step is performing a contrast-enhanced MRI of the brain and/or spine [9, 16]. Our patient had a cerebellar lesion with cortico-pial hypersignal in FLAIR, with post-gadolinium T1-enhancement (Figures 1 and 2). Similarly, Van de Ven et al. [16], found that 4 in 9 patients with cerebral contrast-enhancing lesions had also leptomeningeal involvement. In the study of Najem et al. [17], brain mass was the most common radiologic finding followed by leptomeningeal enhancement (10%). Differential diagnoses included metastases, carcinomatous meningitis, multilocular glioma, high-grade glioma, and lymphoma [16]. Afterward, a lumbar puncture should be done (if not contraindicated) for CSF collection, including leukocyte differential count, protein electrophoresis, glucose, and flow cytometry (if suspected hematological malignancy) [16]. All CVID patients with non-infectious CNS lesions had a nonspecific CSF examination: 75% of patients had a mild protein elevation and 75% had a mild mononuclear/lymphocytic pleocytosis [9]. Glucose consumption is not typical of this manifestation, making it more pertinent to exclude an infectious etiology, especially tuberculosis, in our case. Thus, an infectious screening must be performed in all patients, including enteroviruses by PCR (especially when dermatomyositis is suspected), VZV and HSV 1 and 2 PCR, TPPA and VDRL, CMV, EBV, HIV, Borrelia's serology, Interferon-gamma release assay for tuberculosis, Brucella, Immunostaining for Trichinella, hydatice (Cryptococcus and Toxoplasma if CD4 counts are low) [16]. If all of this work-up remains inconclusive, a brain biopsy is recommended [16]. In two case reports similar to ours, with CNS and pulmonary manifestations of CVID, a brain biopsy was performed [4, 7]. However, histological findings were nonspecific, showing focal infiltration of macrophages and lymphocytes, predominantly T-cells [7]. In our case, a brain biopsy was not pursued as the risks outweighed the benefits, and the remaining study was not suggestive of an expansive lesion.

Table 2

Summary of suggested approach to patients with suspected CVID-associated neurological manifestations

A. When confirmed/suspected CVID with neurological manifestations
<ol style="list-style-type: none"> 1. Personal history of increased susceptibility to infection (recurrent infections) 2. and/or family history of antibody deficiency 3. and/or previous history of autoimmune manifestations (frequently autoimmune thrombocytopenia, autoimmune hemolytic anemia, pernicious anemia, and rheumatoid arthritis) 4. and/or presence of granulomatous disease 5. and/or unexplained polyclonal lymphoproliferation
B. Search: immunoglobulin isoforms (IgG, IgA, IgM) - forward to an immunoallergy appointment to exclude other forms of hypogammaglobulinemia
C. Neurological manifestations of CVID (adapted from Van de Ven et al. (16))
C1. Diagnostic evaluation:
<ul style="list-style-type: none"> • Brain imaging – ideally contrast-enhanced MRI: frequently brain mass lesion, followed by lesions with hypersignal in FLAIR and post-gadolinium T1-enhancement • Cerebrospinal fluid – include leukocyte differential count, glucose, protein electrophoresis, and flow cytometry (if suspected hematological malignancy) • Infectious screening in all patients: always enteroviruses (PCR), VZV and HSV 1 and 2 (PCR), TPPA and VDRL, CMV, EBV, HIV, Borrelia's serology (Lyme disease), Interferon-gamma release assay from tuberculosis, Brucella, Immunostaining for Trichinella, hydaticea (cryptococcus and toxoplasma when CD4 counts are low), JC virus (according to the imaging finding) • If the all work-up remains inconclusive, a brain biopsy is recommended • Screening other systemic manifestations (CT TAP, PET) • Molecular testing for underlying genetic CVID
C2. Treatment
<ol style="list-style-type: none"> 1. High (1 mg/kg BW/day prednisone equivalent) or medium-dose (0.5 mg/kg BW/day) steroids, tapering within 4 to 6 weeks to 20 mg/d and then maintenance of 5 mg daily or stopping if responsive 2. In life-threatening or refractory disease: methylprednisolone pulse therapy at a dose of 1g for 3–5 days, dexamethasone or additional immunosuppressants (for example cyclophosphamide). Some studies used methylprednisolone iv 1g for 3–5 days + immunoglobulin replacement therapy - if a rapid response is required, use high-dose intravenous immunoglobulin (1–2 g/kg in 5 days) <p>After 1. and 2. keep low dose of corticosteroids; consider a corticosteroid-sparing maintenance immunosuppressive drug, such as methotrexate, rituximab (good responses in GLILD and associated cerebral manifestation) or infliximab (this last one with low evidence), to reduce the dose of steroid and thus its adverse effects</p>
C3. Follow-up
<ul style="list-style-type: none"> • At each visit, clinical assessment for neurological symptoms • Contrast-enhanced MRI brain and/or spine every 2-3 y or when clinically relevant

When diagnosing CVID, it is also important to look for additional organ manifestations [16]. Finally, Van de Ven [16] recommended, if possible, a genetic evaluation for all patients with CNS disease (search for mutations in ADA2, NFKB1, and CTLA4), since targeted therapies are under investigation.

Overall, the diagnosis of CVID-associated neurological manifestations took an average of 2.5 years, 5.75 years after the onset of symptoms [9]. In our case, refractory headache with intracranial hypertension led to the prompt diagnosis of neurological involvement; however, only after lesion recurrence, 5 years later, was associated with CVID. The wide range of differential diagnoses delays the diagnosis, with neurosarcoidosis being the main mimicry of CVID [4, 7, 9, 11, 20]. Although clinical manifestations can be similar, the key difference between CVID and sarcoidosis are the low immunoglobulin levels in CVID and the normal or high immunoglobulin levels in sarcoidosis [9]. Note that ACE levels do not discriminate CVID and sarcoidosis [8].

Pulmonary involvement is more common than neurological involvement in patients with CVID [7]. GLILD is a specific subtype of interstitial lung disease associated with CVID, characterized by granulomas and/or benign diffuse lymphocytic infiltrates in the pulmonary parenchyma [21]. This disease is often unrecognized and misdiagnosed by physicians [21]; however, it represents a common organ manifestation of CVID, with a prevalence of 8-22%. It is the type of lung involvement in CVID with the worst prognosis [7, 18]. Although a thoracic CT is required to support its diagnosis, there is no specific radiological feature sufficient to confirm this diagnosis [7]. GLILD can be detected on lung biopsies many years before the CVID diagnosis [2]: noncaseating granulomas and lymphocytic infiltrates (as happened in our patient) were consistent features; interstitial fibrosis with architectural remodeling is also frequent [21]. Thus, exclusion of other potential pulmonary pathologies, such as organizing pneumonia, mycobacterial infection, malignancy, and lymphoma, is a key consideration in the diagnosis of GLILD, and it is frequent to consider these patients as having uncomplicated sarcoidosis [8, 21]. There are clues, although not definitive, for the distinction of these two pathologies: 1) concurrent autoimmune disease, such as autoimmune cytopenias, occurs much less frequently in sarcoidosis than CVID [20]; 2) sarcoidosis is more commonly associated with uveitis and skin disease [20]; 3) scattered nodules with areas of consolidation and ground glass, prominent on the lower zones, and numerous bronchiectasis, and compatible biopsy features favored a diagnosis of GLILD instead of sarcoidosis; 4) GLILD patients usually also exhibited almost normal physiologic function (some patients could have a restrictive pattern of pulmonary function tests) [7, 8].

To date, there is no established standard of care for the treatment of patients with CVID, particularly with GLILD or neurological complications [16]. In patients with CVID with neurological or other associated symptoms, and/or evidence of a decline in lung function, after exclusion of infectious and malignant causes, treatment with steroids seems to be safe and effective control neurological manifestations [16]. IVIg replacement is the recommended therapy for symptomatic CVID patients, and it seems to be relevant in the prevention and treatment of GLILD complications, as was evident in our case.

According to Van de Ven et al. recommendations [16], in the acute phase, high or medium-dose steroids (depending on the case's severity) should be used, tapering within 4-6 weeks to 20 mg/day, subsequently maintaining a low dose of corticosteroid therapy or stopping if responsive. In life-threatening or refractory diseases, most patients acutely received high-dose intravenous glucocorticoids, specifically, methylprednisolone at a dose of 1g initially for 3–5 days, as well as immunoglobulin replacement therapy [2, 4, 7, 9–12, 14, 16] - if a rapid response is required, authors use high-dose intravenous immunoglobulin (1–2 g/kg in 5 days) [16]. Only in one case IVIg was used without concomitant corticosteroid therapy [15]. Some authors consider a corticosteroid-sparing maintenance immunosuppressive drug, such as methotrexate [5, 7, 9], infliximab [11] or rituximab [4], to reduce the dose of steroid and thus its adverse effects, with good results. In particular, some recent studies have shown that rituximab in combination with prednisolone represents an effective therapy for GLILD, also achieving clinical and MRI-morphological regression of the neurological manifestation of CVID [4, 18, 22]. Even though the major part of its immunomodulatory effects are accountable to B-cell depletion, rituximab may also target both helper and cytotoxic T-cells, increasing the T regulatory cells and normalizing of Th1/Th2 ratio [22]. These effects support its use as a second line in autoimmune and lymphoproliferative complications of CVID [22]. In relation to infliximab, it had mixed results in CVID patients with neurological manifestations [18]. Reports suggest that a synergistic effect of intravenous immunoglobulin and infliximab improves neuroimaging as well as systemic features such as fever, night sweats and lymphadenopathy, whilst having no clinical effect on neurological deficits [18].

In case of detection of a specific mutation, studies report better results with targeted therapy: patients with DADA2 mutations may be candidates for anti-TNF therapy, with CTLA-4 or LRBA mutations for abatacept, those with a gain of function mutations of GOF-PIK3CD or loss of function LOF-PIK3R1 (APDS 1 and 2) may improve with mTOR inhibitors, like rapamycin, or newer agents such as Idelalisib [1].

For the follow-up study, Van de Ven et al. [16] recommend performing a contrast-enhancement MRI at least every 2-3 years, or if relapse is suspected. In the described cases of neurological manifestations of CVID, patients had generally a good prognosis, with clinical and imaging remission in the majority within three months, as long as the therapy with steroids and immunoglobulins was maintained [9]. However, these patients have a high relapse rate after treatment interruption [16], as happened with our patient. Ameratunga et al. [23] had recently described a disease severity score for CVID and CVID-like disorders (CDSS). The CDSS focuses on cumulative damage caused by CVID, divided into three categories - mild, moderate, and severe. Mortality is increased in patients with functional or structural lung disease or hepatitis [23]. In our patient, damage to the CNS is unlikely to result in mild complications, most are likely to be life-threatening or have the potential to cause severe disability [23]. Our patient scored 10 (severe disease) in CNS manifestations, 5 in pulmonary parameters (mild GLILD, mild bronchiectasis), and 1 for asymptomatic splenomegaly, out of a total of 16 in the CDSS severity score.

In conclusion, a CVID-associated neurological disorder is a rare but often severe manifestation. Its diagnosis is based on a combination of compatible clinical, radiological, and histological features; exclusion of other pathologies, such as malignancy, lymphoma, mycobacterial disease, and sarcoidosis, should be carried out in all cases. Symptomatic CNS disease appears to respond rapidly to treatment with high-dose steroids, but relapses occur in a considerable number of patients if treatment is discontinued; therefore, follow-up is of utmost importance.

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Figures

Figure 1

Brain imaging. Panel A: non-enhanced (a) and contrast-enhanced (b) Brain CT (April 27/2015) showing two contrast-enhanced lesions in the right cerebellar hemisphere, perilesional edema, obstructive hydrocephalus, and brainstem compression. Panel B: Brain MRI (April 28/2015) showing high signal in both cerebellar hemispheres (right predominance), associated with edema, cerebellar folia effacement, left fourth ventricle compression, superior cerebellar vermis deviation, dehiscence of the cerebellar tonsils (right predominance), and enlargement of the supratentorial ventricular system, and the cortico-subcortical region of the right inferior medial temporal lobe. (c) axial FLAIR, an arrow with a corresponding abnormal focal area of enhancement shown on the (d) axial T1 post-gadolinium images. These lesions had no restriction to diffusion (e and f). Panel C: MRI while the patient was on treatment (May/2015, one month after) showing reduction in the corticopial enhancement areas, without ventricular dilatation, in (g) axial FLAIR and (h) T1 post-gadolinium. Panel D: One year after, 2016, MRI also showing control of brain disease in (i) axial FLAIR and (j) T1 post-gadolinium.

Figure 2

Repetition of the cerebral and pulmonary study in suspected CVID manifestations recurrence. Brain MRI (June 2020) showing a new corticopial enhancement mainly in the inferior aspect of left cerebellar hemisphere, with pachymeningeal enhancement in the cerebellar tent, in (a) axial FLAIR, (b) T1 post-gadolinium, without restriction to diffusion (not shown). Image (c) showing brain MRI (August 2020) with the return of Ig replacement and high-dose corticosteroid therapy. PET/CT study (June 2020) showing (d and e) increased FDG-F18 uptake and heterogeneous distribution of cerebellar FDG-F18, and (f and g) irregular densifications in both lungs and mediastinal-hilar bilateral ganglion formations.