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Original Article

Structural Noninfectious Manifestations of the Central Nervous System in Common Variable Immunodeficiency Disorders

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What is already known about this topic? Central nervous system (CNS) involvement in common variable immunodeficiency (CVID) disorders is a rare but often severe disease manifestation.

What does this article add to our knowledge? CVID patients with CNS disease frequently have other disease manifestations, particularly autoimmune cytopenia and lymphoproliferation. Contrast-enhancing lesions of the brain and/or myelon were the most common findings on magnetic resonance imaging.

How does this study impact current management guidelines? Diagnostic evaluation aiming to rule out infectious causes is mandatory; a genetic evaluation is strongly recommended because the probability for an underlying monogenic disorder is high.

BACKGROUND: Central nervous system (CNS) disease in adult common variable immunodeficiency (CVID) is rare, and therefore diagnostic and therapeutic protocols are lacking. OBJECTIVE: To provide clinical information aiming to establish awareness and first experience-based recommendations. METHODS: We reviewed clinical manifestations, genetic and immunological characteristics, diagnostic evaluation, and treatment of patients with CVID with abnormal magnetic resonance imaging (MRI) of the CNS disease in our cohort. RESULTS: Seventeen patients with CNS manifestation and a previous diagnosis of CVID were identified. Presenting symptoms of the CNS disease included loss of sensory or motoric function, headache, or epilepsy. Contrast-enhancing lesions of the brain or solely the spinal cord were the most common findings on MRI. The prevalence of splenomegaly, lymphadenopathy, interstitial lung disease, and autoimmune cytopenia was significantly increased compared with control CVID patients. In 8 patients, a molecular defect was identified, including mutations in *CTLA4*, *NFKB1*, and *CECR1*. Patients with CVID with CNS involvement generally displayed lymphopenia, skewed $CD4^+$ T-cell subsets, and increased proportions of $CD21^{low}$ B cells in the peripheral blood. CNS involvement usually responded well to high-dose steroids, but regularly required maintenance therapy to prevent relapse. CONCLUSION: CNS disease is a severe but rare complication in CVID disorders, particularly affecting patients with other noninfectious disease symptoms. Diagnostic evaluation needs to rule out infectious causes by all means; a genetic evaluation is recommended given the high probability of an underlying monogenic disorder. Possible treatment consists of steroids with

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Abbreviations used
ADA2- Adenosine deaminase2
CID- Combined immunodeficiency
CNS- Central nervous system
CSF- Cerebrospinal fluid
CTLA4- Cytotoxic T-lymphocyte–associated antigen 4
CVID- Common variable immunodeficiency
DADA2- Deficiency of adenosine deaminase 2
HSCT- Hematopoietic stem cell transplantation
ICD- International Statistical Classification of Diseases
IgRT- Immunoglobulin replacement therapy
ILD- Interstitial lung disease
JCV- John Cunningham virus
LRBA- LPS-responsive beige-like anchor protein
MRI- Magnetic resonance imaging
NGS- Next-generation sequencing
PCR- Polymerase chain reaction
PID- Primary immunodeficiency
PML- Progressive multifocal leukoencephalopathy
Treg- Regulatory T cell

yet to be determined optimal maintenance therapy in case of relapse. **(J Allergy Clin Immunol Pract 2020;8:1047-62)**

Key words: *Primary immunodeficiency; CVID; Common variable immunodeficiency; Central nervous system; Encephalitis; MRI; Myelitis*

Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency (PID) characterized by reduced serum immunoglobulins, recurrent bacterial infections, and an impaired response to vaccinations.[1] Infections of the central nervous system (CNS) are rare and after initiation of immunoglobulin replacement therapy (IgRT) usually limited to rare viral infections,[2,3] including polyomavirus John Cunningham virus (JCV) triggering progressive multifocal leukoencephalopathy (PML).[4-7]

More than a third of patients with CVID develop noninfectious disease-related complications due to disturbed control of immune activation.[8] These complications include hematologic malignancies, autoimmune cytopenia, lymphadenopathy, granulomatous disease, interstitial lung disease (ILD), and inflammatory or autoimmune enteropathy.[8,9] Histological biopsies of affected tissue often show a lymphocytic infiltration of various compositions, whereas plasma cells are generally lacking. In some cases, the disease progresses to a late-onset combined immunodeficiency (CID, or LOCID) characterized by severe $CD4^+$ T-cell loss and occasional opportunistic infections.[10]

In the recent years, several new genetic defects associated with hypogammaglobulinemia and immune dysregulation have been identified in patients who fulfill the diagnostic criteria of CVID. Cerebral involvement was described in deficiency of adenosine deaminase 2 (DADA2),[11] cytotoxic T-lymphocyte–associated antigen 4 (CTLA4),[12,13] protein kinase C delta,[14-16] DNMT1,[17] and with gain-of-function mutations in signal transducer and activator of transcription STAT1.[18,19] Autosomal recessive DADA2 was first described as a fever syndrome with livedo-like rash and early onset strokes, later additional phenotypes included a CVID-like disorder, and 18% of patients suffered from additional CNS involvement.[20] Haploinsufficiency of CTLA4, an inhibitory receptor expressed on activated and on $FoxP3^+$ regulatory T cells (Treg), leads to impaired Treg function and uncontrolled immune activation. CNS manifestations have been described in at least 14 of 90 patients in a recent cohort.[21]

In selected patients of our CVID/CID cohort, we observed intracerebral disease on magnetic resonance imaging (MRI) that was not of infectious, atherosclerotic, or malignant origin. When excluding aseptic meningitis secondary to IgRT,[22] cerebral involvement in CVID is rare and mostly only described in sporadic cases.[23-26] Clinical manifestations include acute disseminated encephalomyelitis,[27] granulomatous disease, and (autoimmune limbic) encephalitis.[28] The DEFI Study Group reviewed granulomatous disease in a cohort of 436 patients with CVID; approximately 0.7% had granulomatous disease of the CNS.[29] A review on intracranial granulomatous disease in CVID found that patients with brain involvement were generally Caucasian, female, and often had pulmonary involvement.[26] Cunningham-Rundles and Bodian[30] reported 3 patients with cerebral atrophy and 1 with PML in a cohort of 248 patients. One patient died of measles encephalitis. Of note, these numbers may be biased by the fact that virus detection can be difficult and therefore challenge the differentiation between viral and noninfectious causes.

In this report, we review the manifestations of patients with CVID with CNS disorders and describe their genetic and immunological characteristics and treatment with the aim of improving early identification and initiate a process establishing diagnostic and treatment strategies of this rare secondary complication in CVID.

METHODS

Eligible adult patients were identified using a retrospective analysis of our clinical database at the Center for Chronic Immunodeficiency Freiburg. Patients diagnosed with CVID according to ESID criteria, related hypogammaglobulinemia, or atypical CID after initial diagnosis of CVID (International Statistical Classification of Diseases [ICD]-10 Codes D 80.0-80.9, 83.0-83.9, and 81.8 or 81.9) were screened for CNS involvement (all ICD-10 Codes with G). Patients identified by ICD screening were then subject to inclusion (noninfectious encephalitis, encephalomyelitis, myelitis, and/or other contrast-enhancing lesions on brain or myelon imaging of unclear origin) and exclusion criteria (overt atherosclerotic cerebrovascular accidents, brain injury due to trauma, and epilepsy without structural abnormalities). Clinical and immunological data were collected. Patients underwent diagnostic evaluation to exclude infectious agents at the time of the event according to the discretion of the treating physician. Organisms sought included *Cryptococci*, *Borrelia burgdorferi*, herpes simplex viruses 1 and 2, varicella zoster virus, human herpes virus 8, cytomegalovirus, Epstein-Barr virus, JCV, and human T-lymphotropic viruses 1 and 2. Flow cytometric data on T- and B-lymphocyte subsets were collected (see Supplementary Methods and Table E2, available in this article's Online Repository at www.jaci-inpractice.org). If multiple tests were performed, the most complete lymphocyte panel close to the date of diagnosis of CNS disease and if available before immunosuppressive treatment was included. Data on immunosuppressive treatment were collected. Treatment with glucocorticoids was categorized into low dose (<20 mg/day), medium dose (>20 mg/day but <0.5 mg/kg body weight), and high dose (>0.5 mg/kg body weight).

After ethical approval by local authorities (Freiburg 239/1999 and 121/11), written informed consent was obtained from all patients.

DNA was collected from 16 patients and used for next-generation sequencing (NGS) as described previously.[13] Detected genetic variants were confirmed by Sanger sequencing.

To compare "CNS patients" to our control CVID population, a second retrospective analysis of the Center for Chronic Immunodeficiency CVID cohort was performed. Clinical and basic laboratory data on all patients with CVID were extracted from our database. Differences between groups were compared using Mann-Whitney *U* tests or Pearson's χ^2 tests for continuous and categorical data, respectively.

RESULTS

CNS involvement is part of multiple disease-related complications

Seventeen patients (9 male, 8 female) with CNS involvement and an initial diagnosis of CVID were identified (Table I). Retrospectively, 4 of these patients did not fulfill the criteria for probable CVID and were diagnosed as "possible CVID"; in 2 of these patients, hypogammaglobulinemia was diagnosed after rituximab treatment, and hence secondary immunodeficiency could not be excluded. The other 2 patients had decreased IgG subclasses before initiation of IgRT.

The majority of patients had no family history for immunodeficiency or CNS disease, except that the mother of patient 2 and the father of patient 3 had mild IgA deficiency. The father of patient 5 had agammaglobulinemia and rheumatoid arthritis. Patient 4 had a sister with a similar clinical phenotype characterized by idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and immune complex vasculitis, but without signs of antibody deficiency. She died after lung transplantation. Patient 13 was the only child of consanguineous origin.

CNS disease preceded the PID diagnosis in 4 patients; in 3 patients, both were diagnosed simultaneously. The CNS disease varied: most common presenting symptoms were loss of motor skills sometimes accompanied by headache or epilepsy (Table I, and more detailed information available in Table E1, available in this article's Online Repository at www.jaci-inpractice.org). In addition, 2 patients presented with hypesthesia and dysesthesia. Three patients were asymptomatic and incidental lesions were found on imaging. Next, we compared the prevalence of noninfectious complications such as autoimmunity in patients with CNS involvement to the entire Freiburg CVID cohort. Age and gender distribution were comparable (controls vs CNS disease; percentage of females 50% vs 47%; mean age 46.6 ± 15 vs 44.1 ± 11.0 years). In patients with CNS involvement, the prevalence of splenomegaly, lymphadenopathy, ILD, and autoimmune cytopenia was significantly increased compared with the control CVID patients (Figure 1). There were no differences observed for CVID-related enteropathy, granulomatous disease, organ autoimmunity, or malignancies. Although numbers are small to draw definite conclusions, there were no relevant differences within the CNS group between patients with a conclusive and a possible CVID diagnosis. Subsequently, we sought to establish a genetic diagnosis using NGS in 16 of 17 patients. We found 8 patients with mutations in known PID-associated genes, as shown in Table I.

Imaging of the CNS disease reveals heterogeneous lesions of the brain and myelon

One or more MRIs were available for 15 patients. No imaging could be retrieved for patient 16, and of patient 7, only a poor-quality cranial computed tomography scan was available. All available images of the brain and spinal cord were reviewed by a dedicated, blinded neuroradiologist (MI, 28 years of experience) (Table I, and Table E1, available in this article's Online Repository at www.jaci-inpractice.org); representative images are shown in Figure 2.

CNS imaging demonstrated several different lesions of brain and myelin. In brief, cerebral contrast-enhancing lesions were the most common finding and could be demonstrated in 9 patients. Four of them had leptomeningeal involvement (Figure 2, *A*). There were 5 patients with contrast-enhancing myelon lesions; 3 of them had exclusive spinal cord involvement (Figure 2, *B*). Furthermore, there were 3 patients with hemorrhagic lesions (Figure 2, *C*): 1 patient with MRI findings compatible with macroscopic vasculitis (Figure 2, *D*) and 2 patients with space-occupying lesions (Figure 2, *E*).

Based on these radiographic findings, patients were divided into 4 subgroups: meningoencephalitis and/or myelitis (n = 9), CNS vasculitis (n = 4), incidental findings of unknown origin (n = 2), and neurosarcoidosis and/or granulomatous encephalitis (n = 2). The 4 patients with CNS vasculitis were generally younger at diagnosis of PID (average 23.7 years) and CNS disease (27.3 years). They all suffered from autoimmune cytopenia and splenomegaly, whereas none of them had lymphadenopathy, ILD, granulomatous disease, or malignancies. This is in contrast to the first subgroup, because the majority of patients with meningoencephalitis and/or myelitis displayed ILD and lymphadenopathy, and 4 of them had granulomatous disease. Malignancies were only found in this subgroup. Furthermore, the 2 patients with neurosarcoidosis/granulomatous disease did not have granulomatous disease at other locations. Their CNS disease was diagnosed before or simultaneously with their CVID. Although the yield of NGS was higher in CNS vasculitis and granulomatous disease compared with the other 2 subgroups, a molecular diagnosis could not predict the clinical phenotype. Of the 2 patients with NFkB1 deficiency, 1 had CNS vasculitis whereas the other one had granulomatous encephalitis. Similarly, the 2 patients with CTLA4 belonged to the meningoencephalitis/myelitis and the CNS vasculitis subgroup.

Diagnostic evaluation of cerebrospinal fluid and histology was often incomplete and inconclusive

Biopsies were available in 4 patients. In patient 4, biopsy of the lesion in the cerebral frontal lobe was compatible with neurosarcoidosis. In patient 12, 2 consecutive biopsies showed diffuse lymphoplasmacellular and macrophagocytic infiltrates. Patient 14 displayed similar findings, whereas patient 17 demonstrated atypical nonmalignant T-cell–rich lymphocytic infiltrates.

Cerebrospinal fluid (CSF) was collected in 12 patients to exclude infections, lymphoma, or plasma cell dyscrasia (Table I, and Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Most patients' CSF showed low or absent immunoglobulins. No monoclonal or oligoclonal bands were detected in any of the patients. Patient 8 was tested for antineuronal antibodies but found to be negative.

An infectious diagnostic evaluation of the CSF was performed to a highly variable extent in 8 patients. Noticeably, besides using polymerase chain reaction (PCR) as a direct diagnostic method, indirect diagnostics procedures by measuring specific antibodies were performed in 4 patients, despite the fact that 2 of them were

TABLE I. Main characteristics of patients with CVID and CID with structural CNS disease

Patient	Gender, age at diagnosis of CVID (y)	CNS diagnosis, age (y) Initial symptoms	Initial MRI findings	Genetic diagnosis	Additional clinical findings	Additional diagnostic findings
1	F 39.5	Meningoencephalitis, 48.5 Headache and vomiting, dysphagia and dysarthria, paresis of the cranial nerves VII, IX, X, XII	Leptomeningeal enhancement of the caudal cranial nerves IX-XI on the left	No mutation	ITP, neutropenia, LAD, granulomatous disease of the lungs, eyes, and parotid glands	CSF: pleocytosis, elevated protein and lactate, intrathecal Ig synthesis, elevated IgG index, positive oligoclonal bands
2	M 24	Myelitis, 34 Headache, neck and back pain, right hemiparesis, and hemihypoesthesia	Contrast-enhancing lesions of cervical and thoracic myelon and leptomeninges	No mutation	AIHA, ITP, splenomegaly, LAD, interstitial lung disease	CSF: pleocytosis, intrathecal Ig synthesis
3	M 16	Encephalomyelitis, papillitis, 20 Migraine, severe neuropathic pain shoulder and extremities, ataxia	Relapsing, remitting, and long persistent lesions in the brain and cervical spine, the most prominent in C3-5	Heterozygous frameshift mutation **CTLA4** (Y177Ffs*8)	AIHA, ITP, splenomegaly, LAD, NLH of the duodenum, lymphocytic terminal ileitis, Hodgkin's disease	CSF: pleocytosis, elevated protein and albumin quotient levels, intrathecal Ig synthesis
4	M 32.5	Neurosarcoidosis, 31 Symptomatic epilepsy	Partially hemorrhagic lesion, cortical and in juxtacortical white matter, brachium pontis and lobus flocculonodularis left without contrast enhancement	Compound heterozygous mutation **LRBA** (S2446* and Q1715*)	AIHA, ITP, splenomegaly, LAD, NLH of the ileum, reticular and nodular lung disease, chronic colitis	CSF: pleocytosis, elevated protein levels Brain biopsy: complying with neurosarcoidosis
5	F 39	Cerebral vasculitis, 48 Ischemic stroke due to cerebral vasculitis with bilateral stenosis of the middle cerebral artery; later depression	Ischemic lesions due to inflammatory stenoses of the arteries of the circle of Willis Contrast enhancement of the vessel wall of the affected arteries. One older hemorrhagic lesion in the right striatum and internal capsule	Heterozygous splice site mutation **NFkB1** (IVS9+2 [T>G])	ITP, splenomegaly, antiphospholipid syndrome, seronegative RA	CSF: pleocytosis, intrathecal Ig synthesis
6	F 23	Incidental white matter lesions of unknown origin, 26.5 Initially asymptomatic, incidental finding; later temporary fine motor disability right hand, burning paresthesia of both thighs	White matter lesions in peripheral and periventricular white matter without contrast enhancement	No mutation	AIHA, splenomegaly, LAD, lymphocytic alveolitis, enteropathy	–

7	F 40	Encephalitis, 55 Asymptomatic, incidental finding	No MRI available	No mutation	AIHA, ITP, splenomegaly, LAD, follicular hyperplasia of bronchial-associated lymphoid tissue, lymphocytic alveolitis, granulomatous disease of the soft palate	–
8	M 49.5	Autoimmune encephalitis, 49.5 Hemiparesis and aphasia, hallucinations and tremor	Dorsal arteriosclerotic plaque left carotid bifurcation	Not assessed	AIHA, ITP, splenomegaly, LAD, NLH of the duodenum, anal carcinoma	CSF: pleocytosis, elevated protein levels
9	M 28*	Myelitis, 48 Spinal syndrome with dysesthesia left leg up to Th5 level	Edema in cervical and thoracic myelon with contrast enhancement in the upper thoracic myelon	Heterozygous nonsense mutation **TACI** (C193*)	AIHA, ITP, splenomegaly, enteropathy	CSF: pleocytosis
10	F 41.5	Myelitis, 42.5 Gait ataxia, hyperreflexia, hypesthesia lower extremities	Edema in cervical and thoracic myelon and contrast enhancement of the cervical myelon and leptomeninx	No mutation	Splenomegaly, (granulomatous) LAD, NLH of the gastrointestinal tract, ileocolitis	CSF: pleocytosis, elevated protein levels
11	M 33	Meningoencephalitis, 32 Ataxia, tetra spasticity with hyperreflexia, symptomatic epilepsy	Contrast-enhancing lesions in deep and peripheral white matter with concomitant FLAIR hyperintensities	Compound heterozygous mutation **MUNC13-4** (c.1820G>C p.Arg607Pro and c.2346_2349del4 p.Arg782SerfsX12)	Splenomegaly, lymphadenopathy, granulomatous lung disease, and granulomatous hepatitis	CSF: pleocytosis, elevated protein levels
12	M 23	Cerebral vasculitis, 22 Headache, nausea, vertigo, nystagmus	Space-occupying, partially resolving, partially relapsing, partially new occurring, contrast-enhancing lesions with leptomeningeal enhancement	No mutation	ITP, neutropenia, splenomegaly	CSF: pleocytosis, elevated protein- and albumin-quotient levels, intrathecal Ig synthesis, positive oligoclonal bands Brain biopsy: complying with vasculitis
13	F 20	Cerebral vasculitis, 21 Right hemiparesis (recurrent), deviation of the tongue	Chronic and one subacute (at age 21.5 y) lacunar ischemia in both thalami, left internal capsule, left caudate nucleus, cerebellar peduncle, without signs of vasculitis, and without contrast enhancement	Homozygous mutation **ADA2/CECR1** (V458D)	Splenomegaly, arthralgia, small fiber polyneuropathy	–

(continued)

TABLE I. *(Continued)*

Patient	Gender, age at diagnosis of CVID (y)	CNS diagnosis, age (y) Initial symptoms	Initial MRI findings	Genetic diagnosis	Additional clinical findings	Additional diagnostic findings
14	F 26*	Incidental white matter lesions of unknown origin, 25 Asymptomatic, incidental finding	Few unspecific FLAIR hyperintensities in peripheral white matter without contrast enhancement and normal diffusion signal	No mutation	AIHA, ITP, splenomegaly, LAD, granulomatous lung disease, enteropathy	Brain biopsy: lymphoplasmacellular infiltrates, signs of connective tissue generation
15	F 13*	CNS vasculitis, longitudinal myelitis and hypophysitis, 18 Paraplegia of the legs and urinary incontinence	Multiple contrast-enhancing and one hemorrhagic lesion in the brain and thoracic myelon	Heterozygous mutation **CTLA4** (c.347T>C, p.I116T)	AIHA, ITP, neutropenia, splenomegaly, autoimmune thyroiditis, colitis	CSF: pleocytosis, elevated protein- and albumin-quotient levels, intrathecal Ig synthesis
16	M 43	Granulomatous encephalitis, 43 Epilepsy	No MRI available	Heterozygous splice site mutation **NFkB1** (IVS22+3(A>G))	Seronegative RA	–
17	M 38*	Encephalitis, 38 Symptomatic epilepsy, right facial nerve paresis, dysarthria, and aphasia	Space-occupying lesion with contrast enhancement in the left frontal lobe	No mutation	AIHA, ITP, neutropenia, splenomegaly, lymphoid interstitial pneumonia	Brain biopsy: atypical nonmalignant T-cell –enriched lymphocytic infiltrates and possibly presence of plasmacells

AIHA, Autoimmune hemolytic anemia; *CID*, combined immunodeficiency; *CNS*, central nervous system; *CSF*, cerebrospinal fluid; *CVID*, common variable immunodeficiency; *FLAIR*, fluid attenuated inversion recovery images; *ITP*, idiopathic thrombocytopenic purpura; *LAD*, lymphadenopathy; *MRI*, magnetic resonance imaging; *NLH*, nodular lymphoid hyperplasia; *RA*, rheumatoid arthritis; *TACI*, transmembrane activator and CAML interactor.
Bold indicates relevant molecular defects.
*"Possible CVID" as based on the criteria of the European Society for Immunodeficiency (https://esid.org/Education/Diagnostic-Criteria-PID).

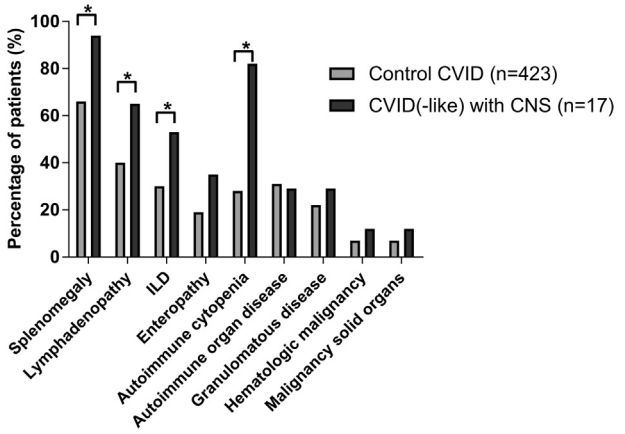

FIGURE 1. Clinical characteristics of CVID(-like) patients with and without structural cerebral nervous system disease. *$P < .05$, Pearson's χ^2 test. *CNS*, Central nervous system; *CVID*, common variable immunodeficiency; *ILD*, interstitial lung disease.

already on IgRT. Causative agents could not be detected; patient 5 had a positive ß-D-glucan in the CSF; however, the panfungal PCR remained negative.

Patients with PID with CNS involvement generally display lymphopenia, skewed CD4+ T subsets, and frequent monogenic defects

We studied immunological phenotypes of patients with CNS disease with the aim of finding common characteristics in affected patients. About half of the patients developed lymphopenia of NK, B, T, or all subsets (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). If not lymphopenic, cell numbers were generally in the lower normal range; none had increased lymphocyte numbers.

In many patients, especially $CD4^+$ T-cell and B-cell numbers deteriorated over time—partly in the context of immunosuppressive therapy, whereas $CD8^+$ T cells tended to be more stable or increase. In general, patients with meningoencephalitis/myelitis had lower numbers of T cells, decreased proportions of $CD4^+$ naïve T cells, and increased proportions of $CD21^{low}$ B cells compared with patients with CNS vasculitis, but patient numbers were too small to draw definite conclusions. For other laboratory markers, for example, soluble IL-2 receptor, associated with lymphoproliferation and possibly granulomatous load in CVID, a temporal relation with the presence, extent, or activity of CNS disease was not observed. Thus, no serological markers associated with the development of CNS disease could be determined.

Next, we compared $CD4^+$, $CD8^+$ T- and B-cell subsets. Among T-cell subsets, a decrease of $CD45RA^+$ naive CD4 T cells was apparent in half of the tested patients (Figure E1, *B*, available in this article's Online Repository at www.jaci-inpractice.org). Treg cells were decreased in 5 of 6 (83%) tested patients. Among $CD8^+$ T cells, naive cells were reduced in some patients whereas effector subsets were rather expanded (Figure E1, *C*, available in this article's Online Repository at www.jaci-inpractice.org).

Studying the B-cell compartment, many patients displayed the characteristic CVID B-cell phenotype with the reduction of class-switched memory cells and plasmablasts and expansion of $CD21^{low}$ B cells in 82% (9 of 11) of patients (Figure E1, *D*, available in this article's Online Repository at www.jaci-inpractice.org).

CNS involvement responds well to high-dose steroids, but regularly requires maintenance therapy to prevent relapse

All patients displayed an apparent antibody deficiency and were treated with IgRT. Thirteen patients (72%) had already received steroids or other additional immunosuppressants for other disease manifestations before the onset of CNS involvement (Table II). Fourteen patients (82%) had symptomatic CNS disease; 12 of them (86%) received immunosuppressive therapy. The induction regimen consisted of medium- (<0.5 mg/kg body weight) or high-dose steroids (>0.5 mg/kg body weight) for most patients (67%). Patients 2 and 15 received high-dose intravenous immunoglobulins in addition to steroids; patient 17 was first suspected of having CNS lymphoma and treated accordingly, including evaluation for stem cell transplantation. Immunosuppressive therapy led to a complete or almost complete response in most patients, whereas 3 of them had considerable residual symptoms.

The median follow-up duration since the initial CNS disease presentation was 5.7 years (range, 1.0-24.1 years). The 3 asymptomatic patients remained asymptomatic. In one, however, progression of granulomatous lesions was seen on MRI while she was on azathioprine therapy for her pulmonary granulomatous disease. The addition of steroids led to improvement, and to date she has been in remission for over 20 years.

Within the symptomatic group, 6 patients (42%) have remained symptom-free after first presentation. The other 8 patients experienced at least 1 relapse during follow-up. The relapses occurred in some patients despite current maintenance immunosuppressive therapy for the CNS disease or other indications (Table II). Treatment of the relapses consisted of renewed high-dose steroids for some patients, whereas patient 5 received 6 cycles of cyclophosphamide, followed by azathioprine. Patient 13 was diagnosed with DADA2 at her second relapse and was started on adalimumab; patient 15 was treated for multiple manifestations of CTLA4 insufficiency with abatacept and eventually received an allogeneic hematopoietic stem cell transplantation (HSCT). She has been in remission since then.

It should be noted that all patients were on immunosuppressive regimens at least at some point during follow-up. Maintenance immunosuppressive therapy specifically for CNS symptoms was initiated after the first flare in only 3 patients. Patients 10 and 12 were started on cyclosporine, whereas in patient 11, cyclophosphamide was initiated. Patient 5 displayed persistent biochemical signs of CNS vasculitis and azathioprine was recommended, but the patient refused and was lost to follow-up.

DISCUSSION

CNS involvement is a rare manifestation in PIDs in general.

Infectious CNS disease is one of the hallmark characteristics of only few PIDs, for example, TLR3 and UNC93B deficiencies, but rarely occurs in CVID.

Reports on inflammatory CNS disease are limited to sporadic cases, and prevalence studies are difficult to establish. In our cohort, the prevalence of inflammatory CNS disease was 4.0%,

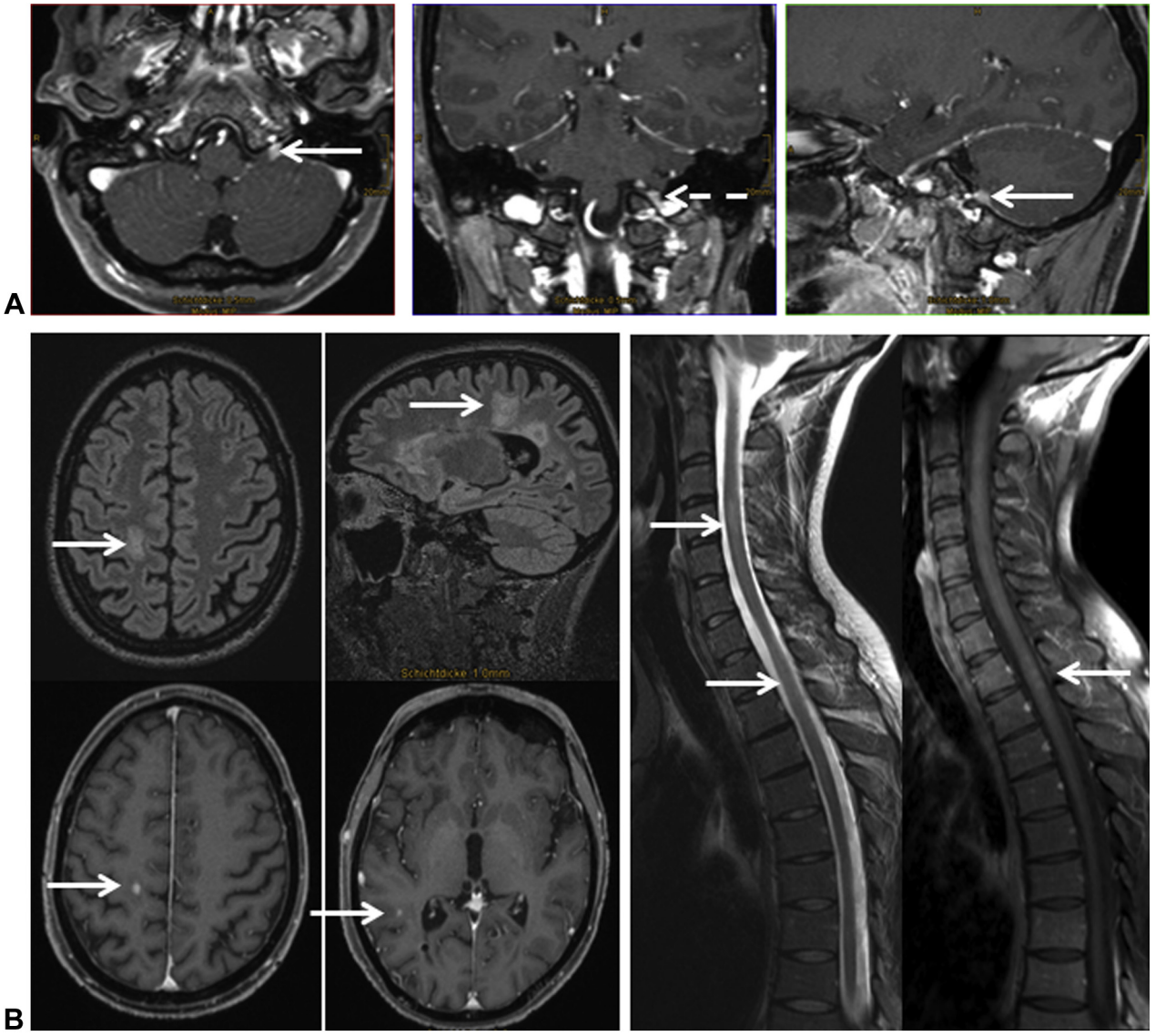

FIGURE 2. Representative images of central nervous system lesions on magnetic resonance imaging. **A**, T1w contrast-enhanced images, patient 1: leptomeningeal contrast enhancement of the caudal cranial nerves IX-XI in the cisternal part (arrow) and in the jugular foramen (dotted arrow), suspected polyradiculitis. **B**, FLAIR, T2w, and contrast-enhanced T1w images, patient 3: contrast-enhancing lesions in the juxtacortical white matter and cervical and thoracic myelon (arrows), suspected myelitis. **C**, T2*-W, contrast-enhanced T1-W of brain and spine, and T2-W of the spine, patient 15: multiple contrast-enhancing and 1 hemorrhagic lesion in the brain and in thoracic myelon (arrows), resolving during the course (not shown). Differential diagnosis: vasculitis, encephalitis, myelitis. **D**, Contrast-enhanced T1-W with fat suppression, patient 5: contrast enhancement of the vessel wall of all basal intracranial arteries, confirming the diagnosis of a vasculitis of the large vessels of the brain (circle of Willis). **E**, FLAIR and contrast-enhanced T1w images, patient 17: space-occupying lesion with contrast enhancement in the left frontal lobe. Differential diagnosis: high-grade glioma, lymphoma, metastasis. *FLAIR*, Fluid attenuated inversion recovery images.

which is higher than previously reported. The differences are possibly explained by the accumulation of complex CVID cases in our center, the high yield of molecular defects associated with CNS disease, and the fact that in some cases active search for CNS disease is required because symptoms can be vague or even nonexistent.

In half of the investigated patients with CNS disease, a genetic diagnosis could be established, which is a higher yield than in the general CVID population.[31] Besides the previously reported CNS involvement in DADA2,[32] the CNS disease was particularly prominent in CTLA4 deficiency. The reported frequency of neurological disease in CTLA4 is 29%; approximately 19% would fulfill our criteria for inflammatory CNS disease.[21] Because LPS-responsive beige-like anchor protein (LRBA) is involved in the regulation of CTLA4 surface expression, it is not surprising that the clinical phenotype of LRBA deficiency is similar to CTLA4 haploinsufficiency. However, to date inflammatory CNS involvement has not been reported in a large series

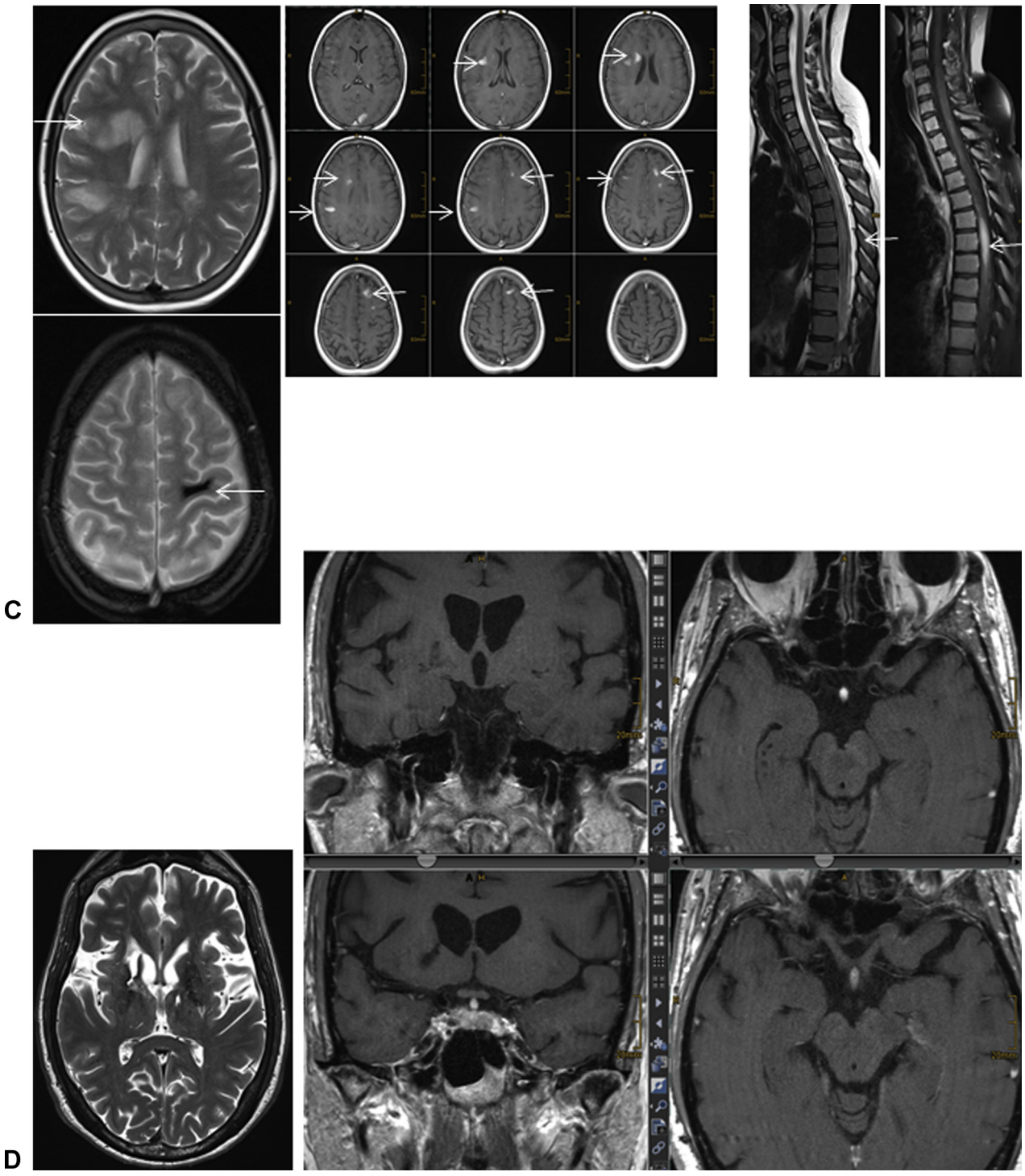

FIGURE 2. (*CONTINUED*).

of LRBA-deficient patients; only 1 of 22 LRBA-deficient patients had a neurological/psychiatric condition not further specified by the authors.[33] In addition to the first case of inflammatory CNS involvement in LRBA deficiency, we also report the first 2 cases of CNS involvement in NFkB1 deficiency.

Najem et al[26] found that CNS involvement was more common in Caucasian patients, females, and patients with lung involvement. Our results confirm that granulomatous CNS disease may precede the PID diagnosis and that lung involvement is common, but we did not see a female preponderance. Actually, in all patients with CNS disease, the disease was part of a more complex phenotype. The presence of splenomegaly, lymphadenopathy, ILD, and autoimmune cytopenia was significantly increased compared with the general CVID population.

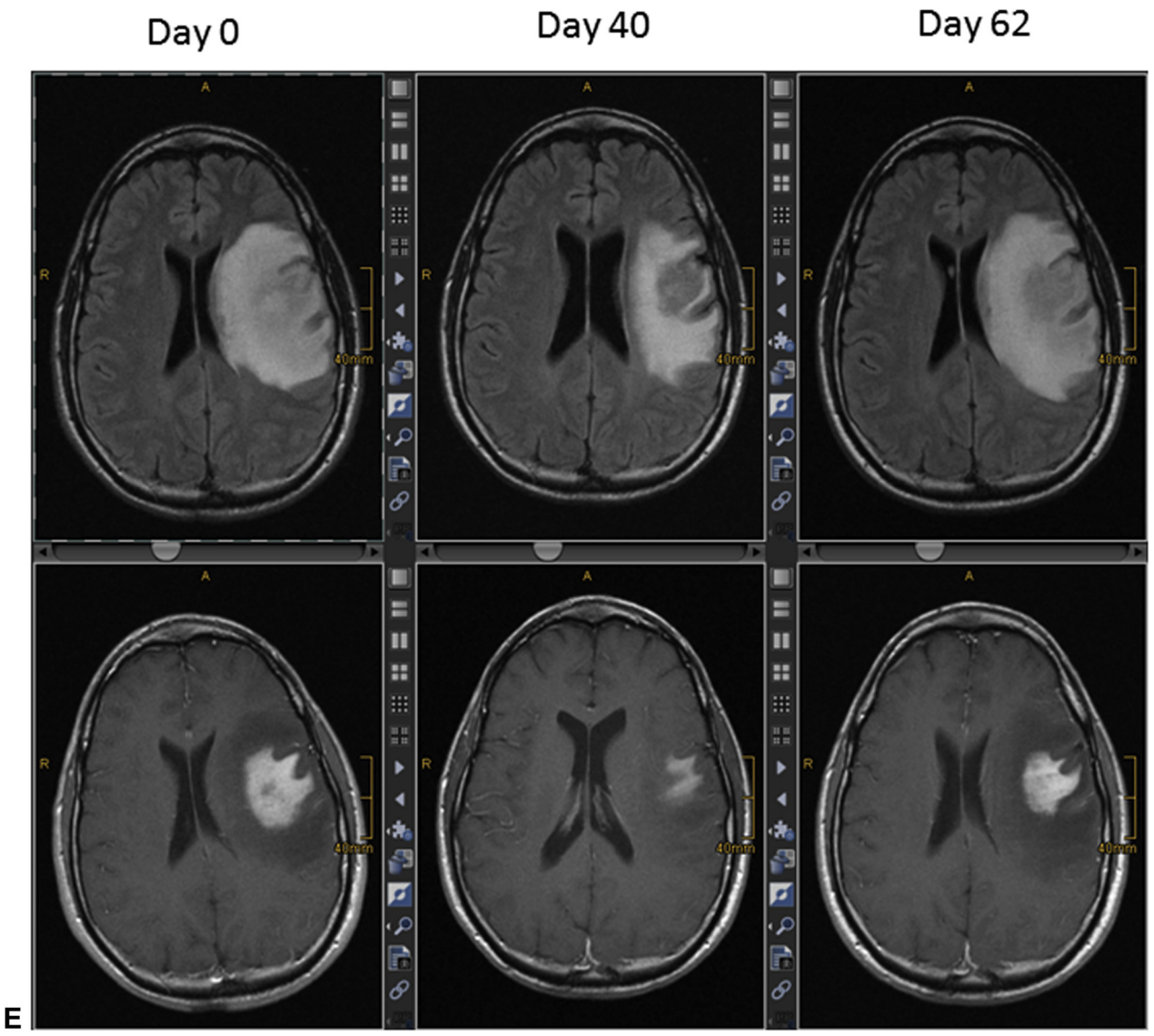

FIGURE 2. (*CONTINUED*).

These findings suggest 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. When we aimed to dissect the CNS population into distinct subtypes, we found that lymphadenopathy and ILD are common in meningoencephalitis and myelitis, which is in line with the case reported by Jabbari et al,[23] but not in patients with CNS vasculitis in our cohort.

Our patients with neurosarcoidosis/granulomatous encephalitis did not have other granulomatous disease, but others found granulomatous involvement of multiple organs.[26,29] The differentiation between natural disease progression or hypogammaglobulinemia and lymphopenia as a byproduct of potent immune suppression cannot be made. Most patients, particularly those with (meningo)encephalitis and/or myelitis, had the typical immune phenotype previously described with a complex form of CVID including lymphopenia, low naïve $CD4^+$ T cells and switched memory B cells, and expansion of $CD21^{low}$ B cells, but routine diagnostics did not reveal a predictive marker for CNS disease. Regarding the CNS-specific diagnostic evaluation, imaging was mostly performed using contrast-enhanced MRI. The neuroradiological spectrum of diagnoses comprised inflammatory lesions such as myelitis, encephalitis, radiculitis, vasculitis, and granulomatous meningeosis. Differential diagnoses were metastases, neoplastic meningeosis, multilocular glioma, high-grade glioma, and lymphoma.

The few brain samples that were collected showed lymphoplasmocytic infiltrates. This finding suggests that the local environment may permit local antibody production so that IgM screening for pathogen-specific antibodies might be reasonable and reveal positive results in some patients. The concomitant use of IgRT in these patients renders diagnostic serologic measurements in the peripheral blood nearly useless. These challenges, combined with the lack of proper diagnostic guidelines, may account for the large variety in infectious evaluation. Hence, we cannot fully exclude the role of certain pathogens in the

TABLE II. CNS disease therapy and response

Patient	Initial therapy and response	Follow-up (FU) since first CNS manifestation, relapse, therapy	Type, chronology, and indication of immunosuppressive therapies*
1	No immune suppression, empiric antibiotics, and antiviral therapy. Improvement of the hemiparesis and other symptoms within few days/weeks. Hoarseness due to incomplete closure of vocal cords lasted longer, almost a year. Still headache and poor concentration after 1 y Almost complete recovery	FU 6 y: no symptoms	−2 y: prednisolone up to 50 mg (ureteral stenosis due to lymph node conglomerate) +3 y: steroids and IVIG (relapse ITP) +3 to 6 y: maintenance prednisolone 2-10 mg/d
2	High-dose steroids, IVIG, antibiotics, antivirals Remission except for hypoesthesia	FU 4 y: **1st relapse** after 16 m, good response on steroids (100 mg prednisolone tapering) and IVIG, also acyclovir and cephalosporins. Tapering prednisolone to 20 mg/d, then **2nd relapse** after 21 m; 100 mg prednisolone 5 d, fast clinical improvement, and finally complete remission. Tapering to maintenance 7.5 mg/d; after 4 y no more active lesions on prednisolone 5 mg/d maintenance	−2 y: high-dose steroids and IVIG (ITP) −1 y: 100 mg prednisolone (ITP) +1 y: RTX (for ITP, 3×)
3	High-dose steroids, then almost complete remission except for urinary incontinence when in deep sleep	FU 18 y: **relapse after unknown, 10, 12, and 15 y**, each treated with steroids, each time more residual damage	−15 to +3 y: azathioprine (AIHA) +3 y: ABVD† chemotherapy (Hodgkin's lymphoma) +10 y<: prednisolone 5 mg/d
4	Remission of CNS lesions (under steroid therapy), since then symptom-free using antiepileptics	FU 23 y: no symptoms while on antiepileptics	−3 to +1 y: steroids (lungs) 0 to 23 y: always on ±5 mg/d prednisolone maintenance therapy
5	High-dose steroids, cyclophosphamide, then complete remission, later azathioprine	FU 5.5 y: first persistent vasculitis signs (CSF lymphocytosis), with thalamus infarct after 6 m, (sub) acute lenticulostriatal infarct after 2 and 3 y high-grade stenosis cerebral artery left and to a lesser extent on the right within increased uptake of radiographic contrast (relapse or related to APS) Eventually stabilizing clinical symptoms under 1× CYC followed by azathioprine **1st (asymptomatic) relapse** after 3 y (new herd on routine MRI), treatment with 6× CYC (patient refused the additional steroids) and then azathioprine. Possibly neurological effects in mental status, concentration, behavior	−9 to −8 y: MTX 15 mg/wk (RA)
6	Not primarily treated, but high-dose steroids to treat AIHA No symptoms, stabile lesions over time on follow-up MRIs	FU 7 y: asymptomatic	−3 y: steroids (AIHA) −3 to +7 y: low-dose steroids since relapse AIHA, at 7 y FU 10 mg/d steroids

(continued)

TABLE II. *(Continued)*

Patient	Initial therapy and response	Follow-up (FU) since first CNS manifestation, relapse, therapy	Type, chronology, and indication of immunosuppressive therapies*
7	Not primarily treated, but 25-50 mg/d prednisone for granuloma palate, skin, and autoimmune cytopenia response	FU 6.5 y: asymptomatic	+3 y: steroids (granuloma palate, nose) +4 y: steroids (suspected dermal sarcoidosis) +5 y: sirolimus (1 m) then stop due to stomatitis, followed by cyclosporine (4 m) but worsening of skin and mucosa, followed by high-dose steroids (3 m), followed by start etanercept; stabilization of mucosa symptoms +6.5 y: high-dose steroids, increased to 25 mg/d because of general clinical deterioration
8	High-dose steroids and initiation of IVIG, complete remission	FU 2 y: relapse after 4 m with status epilepticus, when steroids were tapered to 5 mg/d no relapse, while on steroid reduction scheme (ITP)	−9 y: steroid (AIHA) −1 y: chemo with mitomycin C and 5 FU (anal carcinoma)
9	High-dose steroids, slow response, mild symptoms left	FU 1 y: no relapse	−20 y: steroids (AIHA) −19.6 y: steroids + azathioprine (relapse AIHA) intermittently paused −16 y: azathioprine (AIHA) −8 y: steroids (ITP) −2 y: azathioprine (AIHA/ITP) 2005
10	Initially high-dose steroids, then fast recuperation of sensibility (maintained hyposensibility of lower legs), delayed response for gait disturbance but almost completely resolved	FU 9 y: no relapse, cyclosporin, and low-dose steroid maintenance for myelitis and other granulomatous disease	0 y: cyclosporin (CNS and other granuloma) and low-dose steroids maintenance 9 y: 5 mg/d prednisolone, 9 mg/d budesonide
11	High-dose steroids, almost complete recovery	FU 3 y: **relapse** after 3 y with epilepsy, treated with high-dose steroids, followed by a rapid response and **2nd relapse**; readministration of steroids but the patient deceased 3 mo later	−1 y: steroids and 5 × 500 mg CYC pulse therapy, followed by oral CYC for 1 y (60 g), followed by MMF (4 m), which was discontinued due to hepatitis and cytopenia. Start MTX (1.5 y), stopped due to neutropenia 1 y: 1 g prednisolone
12	Improvement under high-dose steroids	FU 7.5 y: **relapse** after 3.5 y with epilepsy (while temporary dose reduction of cyclosporine from 150 to 75 mg/d) treated with additional high-dose steroids. **2nd relapse** after 4 y; treatment with steroids and CYC was negated by the patient. After 6.5 y **3rd relapse** with generalized epilepsy while using cyclosporine A 75 mg; CYC was advised but refused by the patient	1 to 4 y: cyclosporine A 75 mg bid (CNS and ITP) maintenance, stopped for unclear reasons. Intermittent use of steroids 1 y: low-dose steroids (3 m) 4 y: 2 × 1000 mg RTX (ITP)
13	Medium-dose steroids, partial response with some residual lesions (motor deficit right hand and ankle; sensory loss of right arm and leg)	FU 2.5 y: **relapse** infarction after 1 m on medium-dose steroids, start adalimumab	−1 y: short period of steroids (inflammation, suspicion of FMF) 0 y: prednisone 25 mg (suspicion infarcts due to ADA2) 0.1 y: adalimumab 40 mg/wk, maintenance prednisolone 5 mg/d; HSCT is being considered

14	High-dose steroids for CNS and various other indications, reduction of granuloma	FU 21 y: asymptomatic	Intermittent steroids for cytopenia −5 y: azathioprine 100 mg (6 m, cytopenia) 1 y: cyclosporine A (2 y, pulmonary granuloma) 6 y: steroids (AIHA) 9 y: azathioprine 150 mg/d, later 200 mg/d (18 m) 11 y: steroids (ITP relapse) 12 y: steroids (ITP relapse) 21 y: 5 mg/d prednisolone maintenance
15	High-dose steroids and IVIG Partial response of paraparesis	FU 4 y: **relapse** after 11 m: hypophysitis with central diabetes insipidus, treated with high-dose steroids and IVIG; abatacept initiated 3 m later, stopped before alloHSCT, which was performed 13 m after relapse	−9 to 0 y : intermittent steroids, IVIG, cyclosporine A, MMF, rapamycine and CYC for AIHA, ITP and neutropenia, azathioprine, sirolimus and cyclophosphamide for ITP, AIHA 1.5 y: abatacept (multiple indications in CTLA4 deficiency) (4 m) 2 y: steroids (colitis) 2.2 y: alloHSCT (multiple indications in CTLA4 deficiency)
16	Only antiepileptic treatment	FU 7.5 y: asymptomatic	−13 y: azathioprine (6 m, RA), discontinued due to erythema. Start sulfasalazine, ongoing −6 y: start MTX 15 mg/wk (RA), tapered to 0 after 5 y, restarted and increased to 20 mg/wk −5 y: HCQ (<1 y), discontinued due to headaches 4 y: MTX 20 mg/wk Intermittent steroid use (RA, chronic diarrhea)
17	High-dose steroids, then 2 cycles of RTX + MTX, then cytarabine (2 gifts) and thiothepa (1×), subsequently G-CSF. Good response	FU 5 y: after 6 mo other seizure but lesion in remission (change in antiepileptics). Since then asymptomatic 5 y: asymptomatic grade I meningioma of the falx	−7 to −5 y: intermittent cortisone (ITP) −3 y: 4 × 750 mg RTX (ITP) −0.4 y: 4 × RTX (ITP) 0 y: 2 cycles of RTX/MTX (CNS non-Hodgkin's lymphoma protocol), followed by AraC/Thiotepa 5 y: low-dose maintenance steroids

ABVD, Adriamycin, bleomycin, vinblastine, dacarbazine; *ADA2*, adenosine deaminase2; *AIHA*, autoimmune hemolytic anemia; *alloHSCT*, allogeneic hematopoietic stem cell transplantation; *APS*, antiphospholipid syndrome; *CNS*, central nervous system; *CSF*, cerebrospinal fluid; *CTLA4*, cytotoxic T-lymphocyte−associated antigen 4; *CYC*, cyclophosphamide; *FMF*, Familial Mediterranean fever; *HCQ*, hydroxychloroquine; *HSCT*, hematopoietic stem cell transplantation; *ITP*, idiopathic thrombocytopenic purpura; *IVIG*, intravenous immunoglobulins; *MMF*, mycophenolate mofetil; *MRI*, magnetic resonance imaging; *MTX*, methotrexate; *RA*, rheumatoid arthritis; *RTX*, rituximab.
Relapses are indicated in bold.
*Time scale is started at 0 y(ears) with first CNS manifestation.
†ABVD chemotherapy consists of adriamycine, bleomycine, vinblastine, and dacarbazine.

TABLE III. First expert opinion–based recommendations for diagnosis, follow-up, and treatment of CNS disease in patients with CVID disorders

Diagnostic evaluation
Contrast-enhanced MRI of brain and/or spine, scored by an experienced neuroradiologist
Cerebrospinal fluid (if no contraindication):*
Leukocyte with differential
Protein electrophoresis (for malignancy)
Glucose
Flow cytometry (in case of suspected hematological malignancy)
Infectious screening:
Regular blood cultures
Screening for Borrelia and mycobacteria
If CD4 counts are low, add Cryptococci and toxoplasmosis
Viral screening: at least HSV1, HSV2, VZV, JC, enterovirus, parecho, HTLV1/2 (consider multiplex nucleic acid amplification if available)
Brain biopsy if previous workup remains inconclusive, rather generous indication: histology, PCR for viral pathogens including JCV and enteroviruses
Screening for additional organ manifestations
Molecular testing for underlying genetic PID
Treatment
High-dose (1 mg/kg BW/day prednisone equivalent) or medium-dose (0.5 mg/kg BW/day) steroids depending on the finding, tapering within 4-6 wk to 20 mg/d and subsequently to maintenance of 5 mg daily or stop if responsive
Consider methylprednisolone pulse therapy, dexamethasone, or additional immunosuppressants (eg, cyclophosphamide) in life-threatening or refractory disease
Personalized therapy based on histological findings (lymphoma, T-cell–mediated encephalitis, etc.) and the patient's monogenic defect (eg, anti-TNF for DADA2, abatacept for CTLA-4 haploinsufficiency or LRBA deficiency)
Follow-up
Clinical assessment for neurological symptoms at each visit
Contrast-enhanced MRI brain and/or spine every 2-3 y or when clinically required
Screening for multiorgan involvement
Disease relapse
Repeat the diagnostic protocol
Repeat treatment; strongly consider adding steroid-sparing maintenance immunosuppressive therapy in the context of other disease manifestations and underlying disease and pathogenesis of CNS lesion (if known)
Consider hematologic stem cell transplantation in certain patient groups

CNS, Central nervous system; *CTLA-4*, cytotoxic T-lymphocyte–associated antigen 4; *CVID*, common variable immunodeficiency; *DADA2*, deficiency of adenosine deaminase 2; *HSV*, herpes simplex virus; *HTLV*, human T-lymphotropic virus; *JCV*, John Cunningham virus; *LRBA*, LPS-responsive beige-like anchor protein; *MRI*, magnetic resonance imaging; *PCR*, polymerase chain reaction; *PID*, primary immunodeficiency; *VZV*, varicella zoster virus.
*If safe and perhaps not required in certain cases, eg, certain space-occupying masses.

development of CNS disease, although the overall good response to steroids implies a noninfectious pathogenesis.

We found no enteroviral CNS infection, but this was not always vigorously excluded. Given the potential risk we would recommend to perform enteroviral PCR in all patients with inflammatory CNS lesions, especially if additional signs of dermatomyositis are present. Toxoplasmosis and JCV should be excluded if imaging appearances are suggestive and may require even biopsy in patients with negative CSF findings, especially given the new therapeutic options recently published in JCV infection.[34-36] The value of multiplex nucleic acid amplification assays in this setting is uncertain but may be useful in some patients. Lymphocytic infiltration of CSF does not discriminate viral from noninfectious encephalitis.

On the basis of the above-mentioned results and our own expertise, we made a first recommendation on minimal diagnostic procedures to follow in case of suspected CNS involvement (Table III). Briefly, MRI of brain and/or spine and CSF investigation are mandatory. If CSF investigations for infectious and malignant causes remain inconclusive, brain biopsy needs to be considered, the most important indication being suspicion of lymphoma and infection, including atypical PML,[5] due to the increased risk of lymphoma and opportunistic infection in PID and frequent use of chronic immunosuppressants. Genetic evaluation is advised for all patients with CNS disease, with mutations in *ADA2*, *NFKB1*, and *CTLA4* showing the strongest prevalence in our cohort.

There is no consensus or data on the optimal treatment of inflammatory CNS disease in CVID disorders. After exclusion of infectious and malignant causes, treatment with steroids seems to be safe. High-dose steroid treatment seems to efficiently control the disease in most patients, but the risk of residual damage and disease relapse suggests additional immunosuppressive therapy in patients with recurrent disease. The best prophylaxis remains unknown, as relapses occurred under mainly T-cell, B-cell, or combined suppression. Extrapolating from single patients, rituximab is unlikely to be effective, unlike what is seen in some patients with multiple sclerosis or patients with transverse myelitis due to aquaporin-4–related disease. Because all patients with CNS involvement also had other manifestations, the immunosuppressive regime needs to be adapted to the combined need of these manifestations.

If available, the molecular diagnosis should guide therapy. For patients with DADA2, anti-TNF blocking agents are recommended. For patients with LRBA or CTLA4 deficiency, abatacept and additional hydroxychloroquine could be of value.[37,38] Targeted therapies for NFkB1 deficiency are to date not available. Depending on the overall clinical presentation of the patient, the detection of relevant molecular defects, and the availability of a matching donor, HSCT should be considered.

Follow-up is required for all patients as the disease often relapsed. We recommend to perform MRI at least every 2 to 3 years and more often if relapse is suspected. Hence, thorough clinical neurological history-taking and examination are required at each visit. All patients who suffer(ed) from CNS disease should be screened for other organ involvement because they usually have or will develop multiorgan disease. On discovery of CNS abnormalities, accurate and complete diagnostics are therefore mandatory not only at initial presentation but also at each relapse.

In conclusion, CNS involvement is a rare but serious complication in patients presenting with CVID or CVID-like disease and appears to be a manifestation of a systemic immune dysregulation, as affected patients generally display other autoimmune and lymphoproliferative manifestations. Lymphopenia is common and lymphocyte subset analysis generally

showed impaired B-cell differentiation and low numbers of naive $CD4^+$ cells. Therefore, the diagnosis of CID must be considered in these patients. Although MRI of the brain seems reasonable even in asymptomatic patients with CTLA4 insufficiency or DADA2, it remains to be seen whether this holds true also for NFkB1 deficiency. If CNS disease occurs, a thorough diagnostic evaluation to rule out malignancies and infections is mandatory, but currently not well defined. Genetic testing for mutations in PID-associated genes has a high yield and is therefore strongly recommended. Symptomatic CNS disease appears to respond rapidly to high-dose steroid treatment, but relapses occur in a considerable number of patients and hence follow-up is of utter importance. After repeated exclusion of malignancies and infections, steroids should be reinitiated and the initiation of a steroid-saving maintenance therapy should be considered, although specific recommendations only exist for certain monogenetically defined disorders.

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ONLINE REPOSITORY

SUPPLEMENTARY METHODS

Peripheral blood mononuclear cells were isolated from peripheral blood using Ficoll density centrifugation as described previously.[E1] Flow cytometry staining was performed with the following antibodies at optimal concentrations: anti-IgD fluorescein isothiocyanate (FITC), anti-IgA phycoerythrin (PE) (both Southern Biotech, Birmingham, Ala), anti-CD20 peridinin-chlorophyll-protein complex (PerCP), anti-CD28 PerCP-Cy5.5 (all BioLegend GmbH, Fell, Germany), anti-CD3 PE-Cy7, anti-CD19 PE-Cy7, anti-CD45RA FITC (all Beckman Coulter GmbH, Krefeld, Germany), anti-CD4 Pacific-Blue, anti-CD8 allophycocyanin, anti-CD21 PE, anti-CD25 PerCP-Cy5.5, anti-CD27 Horizon V450, anti-CD31 PE, anti-CD38 PerCP-Cy5.5, anti-CD127 Alexa-Fluor 647 (all BD Biosciences, Heidelberg, Germany), anti-IgM Cy5 (Dianova GmbH, Hamburg, Germany). Six-color data acquisition was performed with a GalliosTM (Beckman Coulter GmbH) or FACSCanto II (BD Biosciences). Data were analyzed using FlowJo (Tree Star, Ashland, Ore) software. T- and B-cell subsets were defined as described in Table E2.

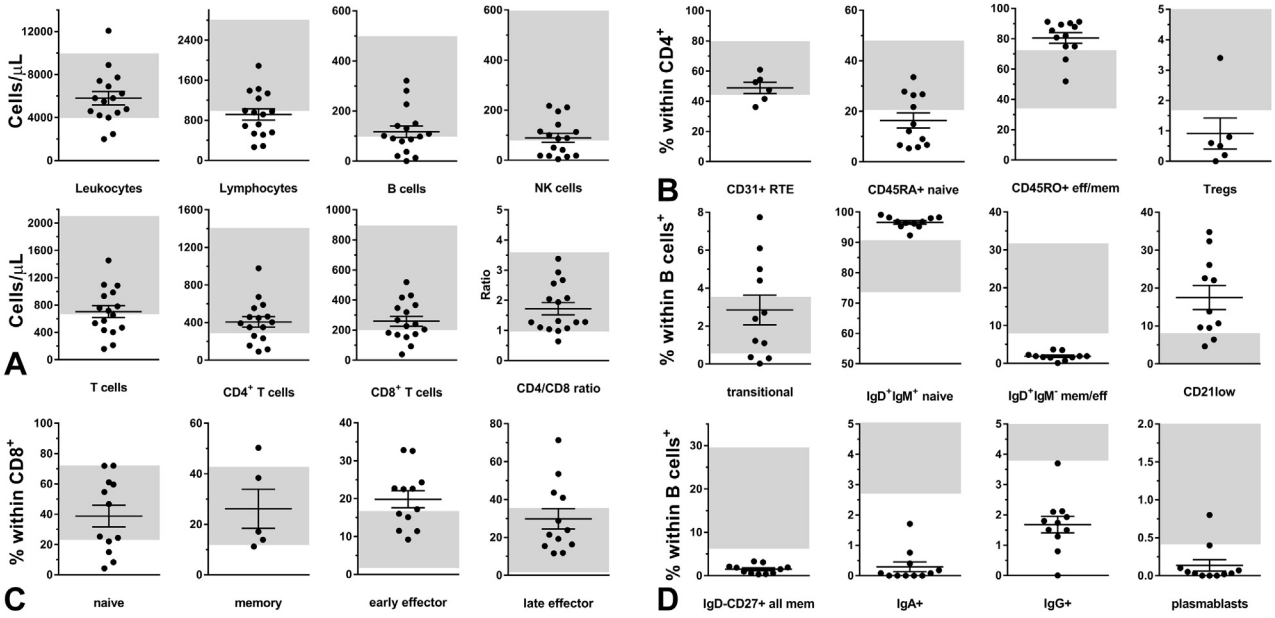

FIGURE E1. Peripheral lymphocyte characteristics of patients with CVID and CID with structural CNS disease. Absolute numbers of lymphocytes (**A**), relative subsets of $CD3^+CD4^+$ T cells (**B**), $CD3^+CD8^+$ T cells (**C**), and $CD19^+$ B cells (**D**). The gray area indicates normal range, and the error bars indicate mean with standard error of mean. *CID*, Combined immunodeficiency; *CNS*, central nervous system; *CVID*, common variable immunodeficiency; *RTE*, recent thymic emigrants; T_{reg}, regulatory T cells.

TABLE E1. Clinical and diagnostic findings of patients with PID with central nervous system disease on MRI

Patient	Gender	CNS diagnosis	Age at PID diagnosis (y)*	Clinical diagnosis	CVID diagnostic criteria fulfilled?	Age at CNS diagnosis (y)	Additional disease manifestations	Genetic diagnosis
1	F	Meningoencephalitis	39.5	CVID	Yes	48.5	ITP, neutropenia, LAD, granulomatous diseases of the lungs, eyes, and parotid glands	No mutation
2	M	Myelitis	24	CVID, progression to LOCID (age 35)	Yes	34	AIHA, ITP, splenomegaly, LAD, interstitial lung disease	No mutation
3	M	Encephalomyelitis, papillitis	16	CVID	Yes	20	AIHA, ITP, splenomegaly, LAD, NLH of the duodenum, lymphocytic terminal ileitis, Hodgkin's disease	Heterozygous frameshift mutation **CTLA4** (Y177Ffs*8)
4	M	Neurosarcoidosis	32.5	CVID, progression to LOCID (age 33)	Yes	31	AIHA, ITP, splenomegaly, LAD, NLH of the ileum, reticular and nodular lung disease, chronic colitis	Compound heterozygous mutation **LRBA** (S2446* and Q1715*)
5	F	Cerebral vasculitis	39	CVID	Yes	48	ITP, splenomegaly, antiphospholipid syndrome, seronegative RA	Heterozygous splice site mutation **NFkB1** (IVS9+2 [T>G])
6	F	Incidental white matter lesions of unknown origin	23	CVID	Yes	26.5	AIHA, splenomegaly, LAD, lymphocytic alveolitis, enteropathy	No mutation
7	F	Encephalitis	40	CVID, progression to LOCID (age 45)	Yes	55	AIHA, ITP, splenomegaly, LAD, follicular hyperplasia of bronchial associated lymphoid tissue, lymphocytic alveolitis, granulomatous disease of the soft palate	No mutation
8	M	Autoimmune encephalitis	49.5¶	CVID	Yes	49.5	AIHA, ITP, splenomegaly, LAD, NLH of the duodenum, anal carcinoma	Not assessed
9	M	Myelitis	28	Possible CVID	No	48	AIHA, ITP, splenomegaly, enteropathy	Heterozygous nonsense mutation **TACI** (C193*)
10	F	Myelitis	41.5	CVID	Yes	42.5	splenomegaly, (granulomatous) LAD, NLH of the gastrointestinal tract, ileocolitis	No mutation
11	M	Meningoencephalitis	33	Initially CVID, later HLH	Yes	32	Splenomegaly, lymphadenopathy, granulomatous lung disease, and granulomatous hepatitis	Compound heterozygous mutation **MUNC13-4** (c.1820G>C p.Arg607Pro and c.2346_2349del4 p.Arg782SerfsX12)
12	M	Cerebral vasculitis	23	CVID	Yes	22	ITP, neutropenia, splenomegaly	No mutation
13	F	Cerebral vasculitis	20	CVID	Yes	21	Splenomegaly, arthralgia, small fiber polyneuropathy	Homozygous mutation **ADA2/CECR1** (V458D)
14	F	Incidental white matter lesions of unknown origin	26**	Possible CVID with progression to LOCID (age 37)	No	25	AIHA, ITP, splenomegaly, LAD, granulomatous lung disease, enteropathy	No mutation
15	F	CNS vasculitis, longitudinal myelitis and hypophysitis	13††	Possible CVID	No	18	AIHA, ITP, neutropenia, splenomegaly, autoimmune thyroiditis, colitis	Heterozygous mutation **CTLA4** (c.347T>C, p.I116T)
16	M	Granulomatous encephalitis	43	CVID	Yes	43	Seronegative RA	Heterozygous splice site mutation **NFkB1** (IVS22+3[A>G])
17	M	Encephalitis	38‡‡	Possible CVID or SAD after RTX	No	38	AIHA, ITP, neutropenia, splenomegaly, lymphoid interstitial pneumonia	No mutation

AIHA, Autoimmune hemolytic anemia; *CMV*, cytomegalovirus; *CNS*, central nervous system; *CSF*, cerebrospinal fluid; *CVID*, common variable immunodeficiency; *DD*, differential diagnosis; *EBV*, Epstein-Barr virus; *FLAIR*, fluid attenuated inversion recovery image; *GAD*, glutamic acid decarboxylase; *HHV*, human herpes virus; *HLH*, hemophagocytic lymphohistiocytosis; *HSV*, herpes simplex virus; *HTLV*, human T-lymphotropic virus; *ITP*, idiopathic thrombocytopenic purpura; *JCV*, John Cunningham virus; *LAD*, lymphadenopathy; *LOCID*, late onset combined immunodeficiency; *MRI*, magnetic resonance imaging; *N/A*, not available or not assessed; *NLH*, nodular lymphoid hyperplasia; *PCR*, polymerase chain reaction; *PID*, primary immunodeficiency; *RA*, rheumatoid arthritis; *RTX*, rituximab; *SAD*, secondary antibody deficiency; *TACI*, transmembrane activator and CAML interactor; *TBE*, tick-borne encephalitis, *VZV*, varicella zoster virus.
Bold indicates relevant molecular defects.
*The age of diagnosis is when the clinical diagnosis of (possible) CVID was made; some patients already had autoimmunity or hypogammaglobulinemia before this diagnosis.
†Results of 5 different CSF samples.
‡These patients were naive to Ig replacement therapy at the time of testing.
§Results of 3 different CSF samples.
‖Clearly increased ß-D-glucan CSF compared with blood; however, this measurement has not been validated.
¶AIHA at age 41.
#Results of 4 different CSF samples.
**ITP and lymphadenopathy at age 15.
††AIHA and ITP at age 9.
‡‡AIHA and ITP at age 31.

TABLE E1. *(CONTINUED)*

CNS symptoms	Initial MRI	Follow-up MRI
Headache and vomiting, dysphagia and dysarthria, paresis of the cranial nerves VII, IX, X, XII	Leptomeningeal enhancement of the caudal cranial nerves IX-XI on the left. DD: polyradiculitis, meningitis	N/A
Headache, neck and back pain, right hemiparesis and hemihypoesthesia. Relapse 1: neck pain. Relapse 2: supraorbital pressure	Contrast-enhancing lesions of cervical and thoracic myelon and leptomeninges. DD: myelitis, meningitis, neoplastic meningeosis	Residual lesion in cervical myelon without contrast enhancement, no cerebral lesions
Migraine, severe neuropathic pain shoulder and extremities, ataxia. Relapse 1: paresis and hypoesthesia of the left leg, incontinence, migraine. Relapse 2: papillitis (left eye) with blurred vision	Relapsing, remitting, and long persistent lesions in the brain and cervical spine, the most prominent in C3-5. DD: encephalomyelitis, multiple sclerosis	Relapsing, remitting, partially longer persistent lesions in periventricular, juxtacortical, deep white matter, infratentorial in cervical and thoracic myelon lesions
Symptomatic epilepsy	Partially hemorrhagic lesion, cortical and in juxtacortical white matter, brachium pontis, and lobus flocculonodularis left without contrast enhancement. DD: multilocular glioma, encephalitis, neurosarcoidosis	Unchanged
Ischemic stroke due to cerebral vasculitis with bilateral stenosis of the middle cerebral artery; later depression. Relapse 1: asymptomatic. Relapse 2: distal paresis of both arms	5 MRIs with ischemic lesions due to inflammatory stenoses of the arteries of the circle of Willis. Contrast enhancement of the vessel wall of the affected arteries. One older hemorrhagic lesion in the right striatum and internal capsule. DD: vasculitis	Contrast enhancement of the vessel wall of all basal intracranial arteries, resolving at age 52.5 y and since there until 53.2 y no new signs of vasculitis and chronic ischemic lesions
Initially asymptomatic, incidental finding. 2-y follow-up: temporary fine motor disability right hand, burning paresthesia of both thighs	From age 22.9 until 26.5 y white matter lesions in peripheral and periventricular white matter without contrast enhancement; cholesteatoma of the left middle ear. DD inflammatory lesions	Recurrent cholesteatoma of the left middle ear. Suspected juvenile recurrent parotitis, DD connective tissue disease
Asymptomatic, incidental finding	No MRI available	N/A
Hemiparesis and aphasia, hallucinations and tremor. Relapse 1: status epilepticus	Dorsal arteriosclerotic plaque left carotid bifurcation. DD: arteriosclerosis	Developmental venous anomaly (anatomic variant) in the left posterior insula
Spinal syndrome with dysesthesia left leg up to Th5 level	Edema in cervical and thoracic myelon with contrast-enhancement in the upper thoracic myelon. DD: myelitis, metastases. Suspected incidental pituitary microadenoma	N/A
Gait ataxia, hyperreflexia, hypesthesia lower extremities. Relapse 1: bilateral paresis of the hip flexors, paraspasticity with progressive reduction of the walking distance	A total of 9 MRIs of the cervical spine: at age 42.5 y, edema in cervical and thoracic myelon and contrast-enhancement of the cervical myelon and leptomeninx DD: myelitis, Devic syndrome, granulomatous meningeosis	Normal brain MRI
Ataxia, tetra spasticity with hyperreflexia, symptomatic epilepsy. Relapse 1: epilepsy	Contrast-enhancing lesions in deep and peripheral white matter with concomitant FLAIR hyperintensities. DD: vasculitis of microscopic vessels, encephalitis	Resolving lesions with hemorrhagic residuals
Headache, nausea, vertigo, nystagmus. Relapse 1: epilepsy. Relapse 2: asymptomatic MRI-progression. Relapse 3: increased intracranial pressure with headache, nausea, vertigo, ataxia	13 MRIs of the brain; space-occupying, partially resolving, partially relapsing, partially new occurring, contrast-enhancing lesions with leptomeningeal enhancement. DD: multilocular glioma, lymphoma, metastases, vasculitis	Age 22: compression fracture of L2 due to a vertebral hemangioma. Age 30: thoracic compression fractures (D 7-9) of unknown origin (osteopenia?)
Right hemiparesis (recurrent), deviation of the tongue. Relapse 1: worsening of hemiparesis, taste disorder, transiently impaired vision right eye. General hyperalgesia	4 MRIs of the brain with several chronic and one subacute (at age 21.5 y) lacunar ischemia in both thalami, left internal capsule, left caudate nucleus, cerebellar peduncle, without signs of vasculitis and without contrast enhancement	5 MRIs of the brain with unchanged findings
Asymptomatic finding	Few unspecific FLAIR hyperintensities in peripheral white matter without contrast enhancement and normal diffusion signal	Unchanged
CNS vasculitis with multiple lesions and longitudinal myelitis leading to paraplegia of the legs and urinary incontinence. Relapse 1: hypophysitis with central diabetes insipidus	2 MRI of the brain and spine and 1 MRI of the brain with multiple contrast-enhancing and one hemorrhagic lesions in the brain and thoracic myelon, resolving during the course. DD: vasculitis, encephalitis, myelitis	1 MRI of brain and spine with small peripheral contrast-enhancing lesions of unknown date and residual lesions in brain and thoracic spine
Epilepsy	No MRI available	N/A
Symptomatic epilepsy, right facial nerve paresis, dysarthria, and aphasia	10 MRIs of the brain: space-occupying lesion with contrast enhancement in the left frontal lobe. DD: high-grade glioma, lymphoma, metastasis	N/A

TABLE E1. *(CONTINUED)*

Patient	Abnormal findings cerebrospinal fluid analysis	Brain biopsy
1	[†]Pleocytosis (28-80 cells/μL): >90% lymphocytes, activated B cells. Elevated protein (562 mg/L) and lactate (1.63 mmol/L) levels. Intrathecal synthesis of IgG and IgM with IgM > IgG. Elevated IgG-index (0.73-1.47), positive oligoclonal bands	N/A
2	Pleocytosis (57 cells/μL): >90% lymphocytes, activated B cells. Intrathecal IgA and IgM synthesis with IgM > IgA	N/A
3	Pleocytosis (27 cells/μL): 90% lymphocytes, 10% monocytes. Elevated protein (523 mg/L) and albumin quotient levels (6.6) Intrathecal IgM-synthesis. CSF cytology: no abnormal findings	N/A
4	Pleocytosis (28 cell/μL): 82% lymphocytes, 1% plasma cells, 15% monocytes Elevated protein level (480 mg/L)	Biopsy of the lesion in the frontal lobe: complying with neurosarcoidosis
5	[§]Pleocytosis (4-8 cells/μL): 70% lymphocytes, 30% monocytes; intrathecal IgM synthesis (3rd sample)	N/A
6	No abnormal findings	N/A
7	N/A	N/A
8	Pleocytosis (8 cells/μL): 4% leukocytes, 55% lymphocytes, 41% monocytes Elevated protein levels (total 90 mg/dL, albumin 65 mg/dL)	N/A
9	Pleocytosis (42 cells/μL): mono- and lymphocytes	N/A
10	Pleocytosis (11 cells/μL): 91% lymphocytes [#]Pleocytosis (7-28 cells/μL): 90% lymphocytes, 10% monocytes Elevated protein levels (760-940 mg/dL)	N/A
11	[#]Pleocytosis (7-28 cells/μL): 90% lymphocytes, 10% monocytes. Elevated protein levels (760-940 mg/dL)	N/A
12	Pleocytosis (67 cells/μL): 90% lymphocytes, 10% monocytes. Elevated protein (841 mg/dL) and albumin-quotient (11.2) levels. Intrathecal IgM and IgA synthesis (IgM > IgA). Positive oligoclonal bands	1st biopsy: samples rich in cells (lymphocytes, monocytes, plasma, and blastoid cells). Negative for CMV, HSV1, HSV2, VZV, enterovirus 2nd biopsy: inflamed tissue rich in cells (lymphocytes, plasma cells, macrophages); histopathology and immune histochemistry complying with vasculitis. Negative for fungi, toxoplasma, tropheryma whipplei, mycobacteria, bacterial DNA, *M. tuberculosis*, CMV, HHV8, VZV, enterovirus, adenovirus, JCV
13	No abnormal findings	N/A
14	CSF: N/A	Lymphoplasmacellular infiltrates, signs of connective tissue generation
15	Pleocytosis (42 cells/μL): lymphocytes and plasma cells. Elevated protein (982 mg/L) and albumin (520 mg/L) levels. Intrathecal synthesis of IgG and IgM (IgM > IgG)	N/A
16	N/A	N/A
17	N/A	Atypical nonmalignant T cell-enriched lymphocytic infiltrates and possibly presence of plasmacells. Monoclonal peak (IgH FR2) within a polyclonal B cell population

TABLE E1. *(CONTINUED)*

Direct (PCR) and indirect (serology) tests performed for detection of microbial/viral agents	Further laboratory tests
CSF: negative for mycobacteria, *Mycobacterium tuberculosis*, mycoplasma pneumonia, bacterial DNA, *Borrelia*, syphilis, CMV, EBV, HSV1, HSV1, VZV, TBE, enteroviruses. Blood: negative for HIV, HTLV1 and HTLV2. Positive for CMV and EBV	Antineural antibodies (Hu, Yo, Ri, cv2/CRMP5, amphiphysin, Ma1 and Ma2) negative
CSF: negative for bacterial DNA, mycobacteria, *M. tuberculosis*, *Borrelia*, syphilis, *Cryptococcus*, JCV, CMV, enterovirus, HSV1, HSV2, VZV. Blood: positive for CMV. Negative for *Borrelia*, syphilis, EBV, hepatitis B	Antineural antibodies (Hu, Yo, Ri, cv2/CRMP5, amphiphysin, Ma1 and Ma2, SOX1 and GAD) negative. Aquaporin 4-antibodies negative
CSF: negative for bacterial DNA, mycobacteria, *M. tuberculosis*, *Borrelia*, syphilis, *Cryptococcus*, JCV, measles, rubella, EBV, HSV1, HSV2, VZV, HHV6, HHV8 Blood: positive for measles, rubella, VZV. Negative for EBV, *Borrelia*, treponema	Antineural antibodies (Hu, Yo, Ri, cv2/CRMP5, amphiphysin, Ma1 and Ma2, SOX1, GAD, Tr) negative. Autoimmune encephalitis antibodies (LGI1, CASPR2, GABA B, NMDA, AMPA 1 and AMPA 2) negative
[†]CSF: negative for *Borrelia*, toxoplasma, fungi Blood: negative for *Borrelia*, *Treponema*, candida, *Aspergillus*, coccidioidomycosis, *Echinococci*, and toxoplasmoa, (Para)influenza, mycoplasma, mumps, HSV, CMV, EBV, measles, rubella, HIV 1-2, Coxsackie and echovirus. Positive for VZV and rubella	N/A
CSF: negative for bacteria, fungi, *Borrelia*, treponema, measles, rubella, VZV, JCV. Positive for ß-D-glucan twice[‡] Blood: negative for *Borrelia*, treponema. Positive for rubella, measles, VZV, CMV	N/A
N/A	N/A
N/A	N/A
[†]CSF: negative for bacteria, *Borrelia*, enterovirus, HSV1, HSV2, VZV Blood: negative for *Borrelia*, treponema, CMV, EBV, TBE, HIV	N/A
CSF: N/A Blood: negative for CMV, HIV, Hepatitis A and B. Positive for EBV, parvovirus B19	Aquaporin 4 antibodies negative
CSF: cultures negative CSF: negative for bacteria, fungi, HSV1, HSV2, *M. tuberculosis* Blood: negative for *Borrelia*, brucella, treponema, enterovirus, CMV, HSV1, HSV2, VZV, TBE, hepatitis A, B and C, HIV. Positive for EBV Stool: negative for enterovirus	N/A
CSF: negative for bacteria, fungi, HSV1, HSV2, *M. tuberculosis* Blood: negative for *Borrelia*, brucella, treponema, enterovirus, CMV, HSV1, HSV2, VZV, TBE, hepatitis A, B and C, HIV. Positive for EBV Stool: negative for enterovirus	N/A
CSF: negative for HSV1, HSV2, VZV, enterovirus, CMV Blood: negative for *M. tuberculosis*, CMV, EBV, *Aspergillus* Stool: negative for enterovirus	Antineural antibodies (Hu, Yo, Ri, cv2/CRMP5, amphiphysin, Ma1 and Ma2, SOX1, GAD, Tr) negative. Autoimmune encephalitis antibodies (LGI1, CASPR2, GABA B, NMDA, AMPA 1 and AMPA 2) negative
N/A	N/A
N/A	N/A
N/A	N/A
N/A	N/A
N/A	N/A

TABLE E2. Flow cytometric description of T- and B-cell subsets

Cell type	Subtype	Name in figure	Gating strategy
Leukocytes			Forward and side scatter
Lymphocytes			Forward and side scatter
NK cells			CD56+CD16+
T cells			CD3+
	CD4+ T cells		CD3+CD4+
		Recent thymic emigrants	CD3+CD4+CD31+
		naïve	CD3+CD4+CD45RA+
		Effector/memory	CD3+CD4+CD45RO+
		Regulatory T cell	CD3+CD4+CD25++CD127−
	CD8+ T cells		CD3+CD8+
		Naïve	CD3+CD8+CD28+CD27+CD45RA+
		Memory	CD3+CD8+CD28+CD27+CD45RA−
		Early effector	CD3+CD8+CD28−CD27+
		Late effector	CD3+CD8+CD28−CD27−
B cells			CD19+
		Transitional	CD19+IgM++CD38++
		Naïve	CD19+IgD+IgM+CD27−
		Effector/memory	CD19+IgD+IgM−
		CD21low	CD19+CD21−CD38-
		Memory (all)	CD19+IgD−CD27+
		IgA memory	CD19+IgA+CD27+
		IgG memory	CD19+IgG+CD27+
		Plasmablasts	CD19+IgM±CD38++

REFERENCE

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