CLINICAL/SCIENTIFIC NOTE

Clinical, Radiologic, and Immunologic Features of Patients With CTLA4 Deficiency With Neurologic Involvement

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Abstract

Objectives

CTLA4 deficiency (CTLA4d) is a disease with multisystem autoimmune features, including neurologic manifestations. We aimed to describe neurologic involvement in these patients.

Methods

We performed a cross-sectional observational study using the French Reference Centre for Primary Immunodeficiencies (CEREDIH) registry plus a surveillance in national society networks. Participants with confirmed CTLA4d and neurologic involvement were included. Clinical, laboratory, and radiologic features were collected, as well as treatments. Available MRI was double-reviewed.

Results

Among 70 patients with CTLA4d, 13 patients (21%) had neurologic involvement. Neurologic symptoms began at a median age of 18 [15–45] years, mostly occurring after systemic manifestations (median delay: 8.5 [4.5–10.5] years). Main symptoms included headaches, focal deficit (54% each), and seizures (38%). MRI detected at least 1 large contrast-enhancing lesion in 8 patients. Lesions reminiscent of multiple sclerosis lesions were found in 6 patients. Cerebellar (6 patients) and large spinal cord lesions (3 patients) were common. Ten patients were treated with abatacept, of whom 9 (90%) showed good clinical and radiologic response.

Discussion

Neurologic involvement is common among patients with CTLA4d. Despite its rarity, and considering the suspected efficacy of abatacept, neurologists should be aware of the characteristics of CTLA4d neurologic involvement.

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Introduction

CTLA4 expression defect (CTLA4d) is caused by *CTLA4* or *LRBA* sequence variations. These Primary Immune Regulatory Disorders are characterized by autoimmune manifestations, chronic lymphoproliferation, and immunodeficiency. The most frequent manifestations are autoimmune cytopenia (mainly thrombopenia and hemolytic anemia), gastrointestinal disorders (chronic diarrhea and inflammatory bowel disease), skin involvement (e.g., psoriasis), lymphoproliferation, or unusual and recurrent infections.[1] The clinical phenotype is variable, including asymptomatic carriers for CTLA4 sequence variation.[1-4] Neurologic involvement is reported in 11%–32% of patients.[5,6] However, a comprehensive description of these patients with neurologic involvement is lacking, as well as the chronological interplay with the other manifestations. Moreover, little is known about the therapeutic effect of CTLA4-Ig fusion protein (abatacept).[7-9]

We therefore conducted a national study to better characterize neurologic aspects and clinical course of this disease.

Methods

We identified all patients diagnosed with CTLA4d in the French Reference Centre for Primary Immunodeficiencies (CEREDIH) registry from 2005 to February 2021.[10] Genetic screening was without charge for patients with suspicious symptoms. In addition, we surveyed neurology and internal medicine national society networks. Participants eligible for inclusion were confirmed CTLA4d patients (by Sanger sequencing), regardless of age, with neurologic involvement, defined as neurologic symptoms with neuroimaging abnormalities, or abnormal CNS imaging alone. Patients with insufficient data were excluded.

Demographic and medical history data, as well as clinical features regarding autoimmune manifestations, lymphoproliferation, unusual infectious manifestations, and neurologic symptoms, were recorded. We also collected all relevant laboratory features (immunoglobulin (Ig) plasma levels, autoantibodies, lymphocyte subpopulations, CSF analysis, and biopsies) and all CNS imaging. All MRI were double-reviewed by 2 experts in neuroimaging (X.A. and C.C.D.), and longitudinal MRI follow-up was reviewed for each patient when available. We recorded treatment modalities.

Statistical Analyses

Descriptive data were presented with medians and interquartile range. All statistical analyses were performed with Prism 8.0.2 (GraphPad Software, San Diego, CA).

Standard Protocol Approvals, Registrations, and Patient Consents

This study received approval from Montpellier University Hospital Institutional Review Board (#202100812). The ethics committee waived participant consent.

Data Availability

Anonymized data not published within this article will be made available by request to the corresponding author.

Results

Seventy patients were identified with CTLA4d, of whom 13 (21%) had neurologic involvement (eFigure 1, links.lww.com/WNL/C995).

Clinical Features and Chronologic Interplay

Table 1 presents all clinical features and age of onset. eTable 1 (links.lww.com/WNL/C997) presents the detailed characteristics of each individual. eAppendix 1 (links.lww.com/WNL/C998) describes 2 clinical vignettes.

Eleven patients presented neurologic symptoms at a median age of 18 [15–45] years. They included treatment-resistant headaches (7 patients, 54%), focal deficit (7 patients, 54%), seizures (5 patients, 38%), and early cognitive decline (patient #3). Five patients displayed a visual impairment related to CNS lesions (n = 3) or optic nerve involvement (n = 2). Four patients had myelitis.

The overall median follow-up was 13.6 [9.6–19.7] years. Figure 1 shows each individual disease course. Most patients (69%) were symptomatic before the age 20 years, but 3 patients (23%) exhibited symptoms after the age 35 years. Autoimmune and infectious manifestations were the first symptoms of the disease in 12/13 patients (92%), with neurologic symptoms occurring after a median time of 8.5 [4.5–10.5] years.

MRI Characteristics

Eight patients (62%) presented ≥1 large contrast-enhancing lesion, located within the supratentorial white matter or cortical and juxtacortical (n = 7 each, 88%) (Figure 2, A1–B4, eFigure 2, links.lww.com/WNL/C996). Cerebellar lesions were identified in 6 patients (75%) (Figure 2, B1–B4). Three patients had ≥1 pseudotumoral (>3 cm) lesion. Leptomeningeal involvement with gadolinium enhancement was observed in patients with cortical lesions and cerebellar lesions (3/7 and 6/6, respectively) (Figure 2, D1–D4). Nine patients had small punctate lesions (Figure 2, C1–C4), reminiscent of multiple sclerosis (MS) for 6 patients (Dawson fingers lesions and ovoid lesions perpendicular to the lateral ventricles) (Figure 2, C3–C4).

Three patients had transverse myelitis (large, contrast-enhancing lesions involving ≥3 spinal cord levels) (Figure 2, E and F).

Biological Features

Laboratory tests (Table 1) mainly showed lymphopenia (77%), hypogammaglobulinemia (69%), and low switched memory B cells with increased naïve B cells.

Table 1 Patient Characteristics

Characteristic	n = 13
Sex, M/F	5/8
Sequence variation, CTLA4/LRBA	12/1
Age of first autoimmune manifestations—y, median [IQR]	6 [3–15]
Age of first infectious manifestations—y, median [IQR]	14 [4–24]
Age of first neurologic symptoms—y, median [IQR]	18 [15–45]
Autoimmunity, n (%)	
Enteropathy	11 (85)
ITP/AIHA/AIN	9 (69)/6 (46)/3 (23)
Cutaneous[a]	8 (62)
Others[b]	5 (38)
Uveitis	3 (23)
Lymphoproliferation, n (%)	
LNE/SM/HM	10 (77)/12 (92)/7 (54)
Other organs	10 (77)
Infectious manifestations, n (%)	11 (85)
Neurologic symptoms, n (%)	
Headaches	7 (54)
Focal deficits	7 (54)
Seizure	5 (38)
Visual field defect	5 (38)
Spinal cord symptoms	3 (23)
Optic neuritis	2 (15)
Cognitive decline	1 (8)
Cancer, n (%)	2 (15)[a]
Granulomatosis, n (%)	7 (54)
Whole blood count features	
Lymphocytes, G/L—median [IQR]	1,113 [750–1,669]
Lymphocytes <1 G/L, n (%)	6 (46)
Eosinophilia, n (%)	2 (15)
Monocytopenia, n (%)	1 (8)
Hypogammaglobulinemia, n (%)	9 (69)
Decreased Ig subtypes, n (%)	
IgG1	3/6 (50)
IgG2	6/6 (100)
IgG3	0/6 (0)
IgG4	4/6 (67)
IgA	11/11 (100)
IgM	6/11 (55)
Autoantibodies, n (%)	
Positive Coombs	6/8 (75)
Organ-specific antibodies	3 (23)
Antinuclear antibodies	1 (8)
CSF analysis	
White blood cells elevation, n (%)	8/9 (89)
White blood cells—/μL, median [IQR]	23 [11–96]
Proteins—mg/dL, median [IQR]	56 [37–106]
Oligoclonal bands, n (%)	5/6 (83)
MRI features, n (%)	
Small punctate lesions	9 (69)
Large contrast-enhancing lesion	8 (62)
Spinal cord involvement	4 (30)

Abbreviation: IQR = interquartile range.
[a] Psoriasis, eczema, or vitiligo.
[b] Two type 1 diabetes, 2 ovaritis, 1 myocarditis, 1 nephritis, and 1 chronic sialadenitis.

Nine patients underwent CSF analysis, commonly showing elevated white blood cell counts (8/9 patients, 89%), increased protein level (6/8 patients, 75%), and oligoclonal bands (OCBs, 5/6, 83%).

Three patients had brain biopsy, all showing polyclonal lymphoproliferative features, in addition to granuloma and vasculitis-like aspects in 1 patient.

Treatment Strategies and Outcome

Most patients received glucocorticoids (GC) (eTable 1, links.lww.com/WNL/C997), at 1–2 mg/kg/d of prednisone equivalent, with an overall good clinical and radiologic response. Seven (54%) patients needed immunosuppressants (eTable 1).

Ten patients received abatacept for neurologic indication or a concomitant systemic manifestation, with a dosing of 500–1500 mg monthly, after a median time of 8.6 [6–13.2] years from neurologic symptoms onset. CNS imaging was available for 9 of these patients. With a median follow-up of 4 [3–12] months, only 1 patient experienced a clinicoradiologic relapse (severe myelitis 4 months after treatment onset). None of the others had new lesion or gadolinium enhancement.

Discussion

Our study confirms that approximately 1 in 5 patients with CTLA4d had neurologic involvement, consistent with

Figure 1 Clinical Course of All Patients

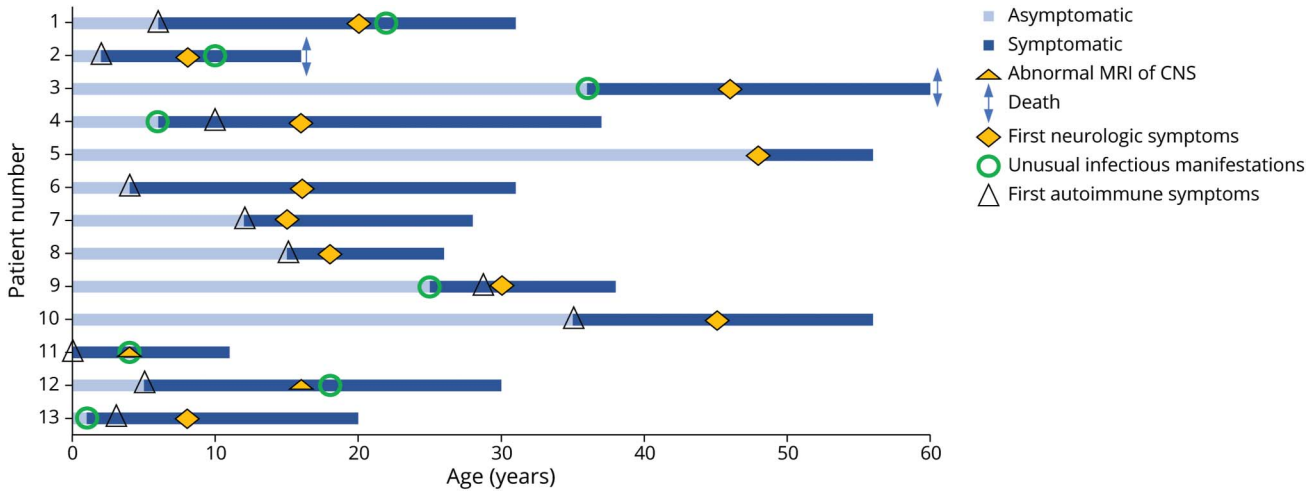
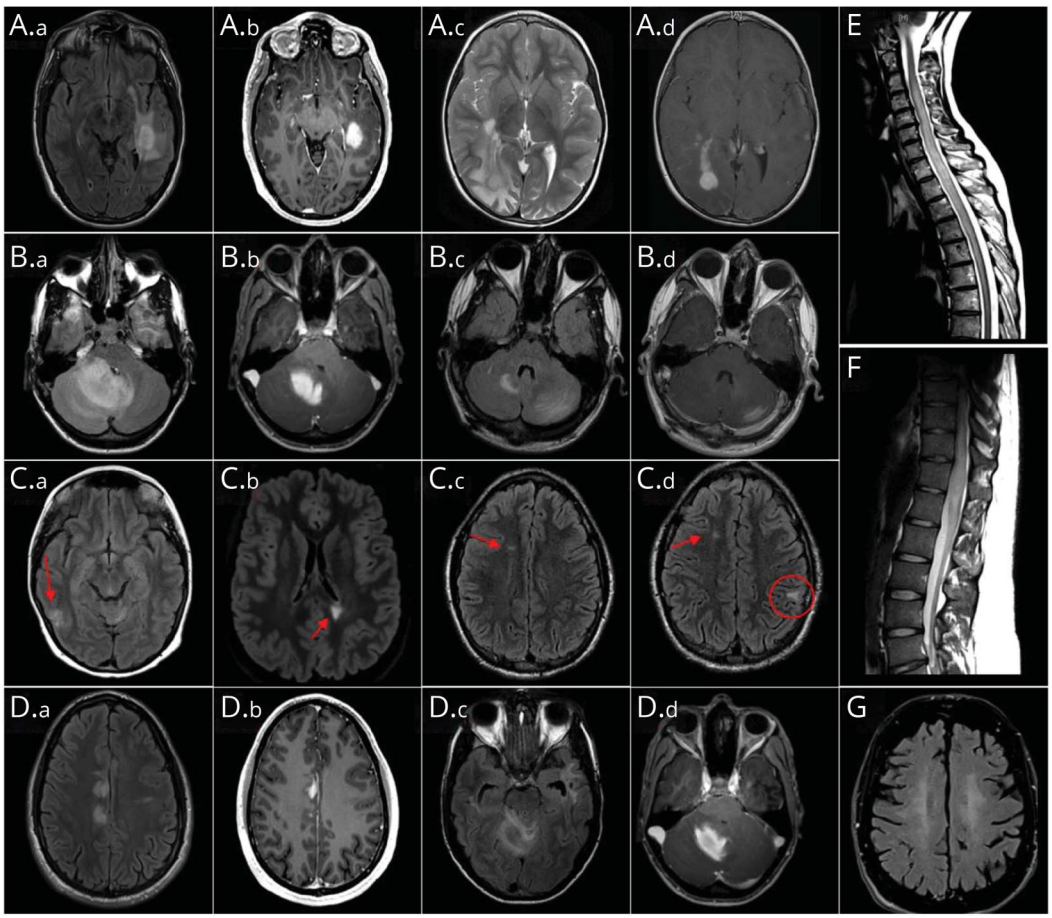


Figure 2 MRI Characteristics of CTLA4d Patients



(A) Large supratentorial lesions (A.a: axial FLAIR; A.b: axial T1 with gadolinium; A.c: axial T2; A.d: axial T1 with gadolinium); (B) large infratentorial lesions (B.a: axial FLAIR; B.b: axial T1; with gadolinium; B.c: axial FLAIR; B.d: axial T1 with gadolinium); (C) small lesions (C.a: small leptomeningeal lesions; C.b: small nonspecific lesion; C.c-C.d: small MS-like lesions); (D) gadolinium enhancement (D.a-D.b: in supratentorial lesions; D.c-D.d: in infratentorial lesions); (E, F) large spinal cord lesions (gadolinium enhancement not shown); (G) diffuse leukoencephalopathy.

previous studies.[5,6,11] We confirm that headaches and seizures are the 2 leading symptoms,[6] but we also report more unusual presentations such as optic neuritis and early cognitive decline.

Although most patients were symptomatic before the age 20 years, 3 patients exhibited late-onset disease, suggesting that CTLA4d should also be considered in adults. Although 92% of patients showed autoimmune and/or unusual infectious manifestations before, neurologic manifestations can happen long after diagnosis. The most frequent neurologic course was characterized by remitting/relapsing focal deficit, but subacute presentation (myelitis and headaches) and slowly progressive presentation (cognitive decline) were also possible. The most characteristic MRI features of CTLAd were large (usually multiple) contrast-enhancing lesions, and the symptoms were disproportionally mild considering the size of the lesions.

Another interesting feature was the relatively high proportion of patients with lesions that could harbor MS-like features. This is particularly important because 1 patient (#5) was eventually diagnosed with MS. However, the identification of similar lesions in other patients from our cohort is intriguing, and it is unclear whether the CTLA4d may have modified the clinical phenotype and disease progression in this patient. These presentations might suggest potential underlying common immunologic mechanisms between CTLA4d and genuine MS.[12] Unfortunately, high resolution susceptibility imaging was not available, precluding assessment of the presence of central vein sign or rim lesions that are considered highly specific for MS.[13]

Regarding therapeutic aspects, literature data suggest that GC are effective both clinically and radiologically.[6,9,11] However, considering the severe effect of long-term GC treatment, the use of GC-sparing agents (e.g., sirolimus and rituximab) is highly recommended.[1,5,11]

We reported a good abatacept treatment response on neurologic features in 9/10 (90%) patients, as suggested previously.[8,9,11] However, because of the concomitant use of GC, more data are needed to assess the specific impact of abatacept on neurologic involvement.

There are limitations in our work, mainly due to retrospective design: MRI acquisitions and follow-up were not standardized. Moreover, because extraneurologic features are often predominant and because of the potential fluctuations in MRI lesions, the exact frequency of neurologic involvement may have been underestimated. Nonetheless, this series is the first to describe detailed chronologic data and the effect of abatacept on the neurologic aspects of CTLA4d.

To conclude, multiple neurologic presentations are not uncommon in CTLA4d, with distinct MRI patterns. Owing to a suspected therapeutic effect of abatacept, early screening and management is recommended. Larger studies could investigate the benefit of early exposure to abatacept in patients with CTLA4d to prevent/slow down the neurologic damage of the disease.

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