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Two neurologic facets of CTLA4-related haploinsufficiency

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Abstract

Objective
To describe the clinical and radiologic neurologic characteristics of patients with cytotoxic T-lymphocyte antigen-4 (*CTLA4*) haploinsufficiency.

Methods
Three patients from 2 families had neurologic manifestations in the context of *CTLA4* haploinsufficiency. Their clinical and MRI findings are presented.

Results
A 16-year-old boy with a previous diagnosis of combined immunodeficiency presented with severe recurrent episodes of headaches, motor deficit, and seizures associated with waxing and waning gadolinium-enhancing FLAIR cortical/juxtacortical hyperintensities. His sister, who also had combined immunodeficiency, had a brain MRI when she was aged 13 years due to recent headaches and transient right hemianopsia. It revealed a gadolinium-enhancing left occipital white matter hyperintensity. Another 49-year-old woman had progressive visual loss and cerebellar ataxia in the context of recurrent pulmonary infections. All 3 patients were found to have inherited *CTLA4* haploinsufficiency. Patient 1's general condition and neurologic manifestations were completely controlled with abatacept (CTLA4-Ig).

Conclusions
These cases suggest that in addition to the variable clinical penetrance and wide spectrum of *CTLA4* haploinsufficiency, its neurologic spectrum is broad, ranging from recurrent tumefactive lesions to progressive deficits including cerebellar ataxia and optic atrophy with leukoencephalopathy. These phenotypes must be recognized, and should lead to a complete immunologic workup, because potentially effective targeted immunotherapy exists.

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Glossary

CTLA4 = cytotoxic T-lymphocyte antigen-4; **ITP** = immune thrombocytopenia.

Cytotoxic T-lymphocyte antigen-4 (CTLA4) is a major negative regulator of T-cell immune response.[1,2] It has recently been shown that heterozygous mutations in the *CTLA4* gene can lead to CTLA4 insufficiency, characterized by a wide range of clinical manifestations including autoimmune diseases, infections, and lymphoproliferation.[3–5] Neurologic manifestations can occur in almost 30% of cases.[5] Nevertheless, their clinical and radiologic characteristics have never been thoroughly described, notably in adult patients.[5,6]

We hereby report on 3 patients from 2 separate families with CTLA4 insufficiency who harbored distinct clinical characteristics, suggesting that its neurologic spectrum is broader than previously suggested.

Methods

Patients were identified from the reference center for adult-onset inherited leukoencephalopathies, Department of Neurology, Montpellier University Hospital, Montpellier, France. Clinical and MRI data were analyzed and are described in the article.

Standard protocol approvals, registrations, and patient consents

Montpellier University Hospital Institutional Review Board approved this study.

Date availability

Anonymized data will be shared by the corresponding author on reasonable request from any qualified investigator.

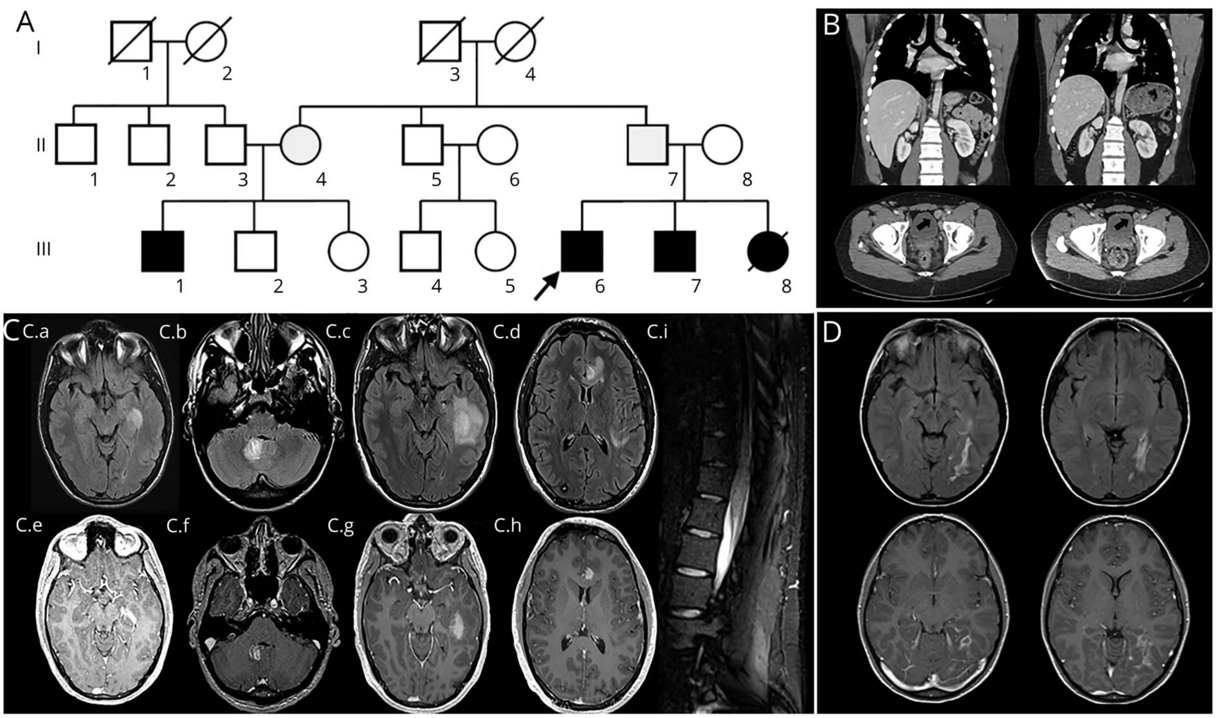
Results

Case reports

Patient 1

A 16-year-old boy (figure 1A, III6) had a previous diagnosis of combined immunodeficiency characterized by autoimmune diseases, repeated skin infections and bacterial pneumonias, and lymphoproliferative disorder (table and figure 1B). The

Figure 1 Family 1



(A) Family 1 pedigree: the arrow indicates patient 1, squares = males, circles = females, black-filled symbol = symptomatic patients, gray-filled symbol = asymptomatic carrier, and strikethrough = deceased patients. (B) Patient's abdominal and pelvic CT showing enlarged liver and lymph nodes (arrow) (left panel), which decreased (respectively from 213 mm to 190 mm and 23 mm to 18 mm) after abatacept therapy (right panel). (C) Regular brain MRI scans repeated from age 16 to 25 years disclosed multiple nodular cortical/juxtacortical FLAIR hyperintensities (C.a–C.d) with gadolinium enhancement (C.e–C.h). (C.i) Spinal cord MRI evidenced diffuse conus medullaris hyperintensities. (D) Patient 1's sister aged 15 years. The MRI showed an infiltrative occipital white matter lesion with gadolinium enhancement.

Table Characteristics of all 3 patients with neurologic involvement

Patient	Patient 1 (III6)	Patient 2 (III8)	Patient 3
Age at onset	5	2	42
Age at onset of autoimmune manifestations	11	2	—
Autoimmune and inflammatory manifestations	ITP	Type 1 diabetes	
	Type 1 diabetes	Evan syndrome	
		Bilateral uveitis	
		Vitiligo	
		Aseptic meningitis	
		Autoimmune ovaritis	
		EBV lymphoproliferative disease	
Autoantibodies	Langerhans islet cell antibodies, antinuclear, antithyroperoxidase, antithyroglobulin, anticardiolipin antibodies, and Coombs test		Rheumatoid factor
Immunologic profile	IgA and IgM insufficiency; low IgG2 and IgG4 subclasses; low T and NK lymphocyte count; low levels of antimeasles and antimumps antibodies	IgG and IgM insufficiency, unmeasurable IgA level; low B and NK lymphocyte count	IgA and IgM insufficiency; reduced IgG2 level and unmeasurable IgG4 level; low B, T, and NK lymphocyte count
Age at onset of repeated infections	5	2	42
Infections	Molluscum contagiosum	Myocarditis (parvovirus)	ENT
	Dermatophytosis	Zona	Lung (bronchiectasis)
	Pneumonias	Pneumococcal meningitis	Papillomavirus
	Anal abscess	Recurrent bacterial pneumonia	
	Septic arthritis		
	Balanitis		
Lymphoproliferative disorder	Yes	Yes	No
	Hepatomegaly and splenomegaly	Hepatomegaly and splenomegaly	—
	Multiple lymph node enlargement	Multiple lymph node enlargement	—
	Interstitial pneumonitis	Kidney infiltrates	
		Interstitial pneumonitis	

Continued

Table Characteristics of all 3 patients with neurologic involvement *(continued)*

Patient	Patient 1 (III6)	Patient 2 (III8)	Patient 3
Age at onset of neurologic symptoms	16	13	49
Neurologic symptoms	Headaches	Headaches	Ataxia
	Weakness	Visual hallucinations	Progressive optic atrophy
	Partial seizures		
Brain and spinal cord MRI	Multiple cortical and juxtacortical lesions, FLAIR hyperintense, with gadolinium enhancement	Infiltrative occipital white matter lesion with gadolinium enhancement	Diffuse, bilateral leukoencephalopathy
			Cerebellar atrophy

Abbreviations: ENT = ear, nose, and throat; ITP = immune thrombocytopenia; EBV = Epstein-Barr virus; NK = natural killer lymphocytes.

immunologic profile was consistent with a combined immune deficiency (table). When he was aged 16 years, he presented with severe recurrent headaches, but a complete workup including a brain MRI was normal. Since that episode, he had recurrent headaches: at age 21 years, a new brain MRI disclosed multiple hyperintense cortical and juxtacortical FLAIR lesions with gadolinium enhancement (figure 1C). Repeated CSF studies disclosed a high white blood cell count (40–150 cells/μL, lymphocytes) and a high protein level (72–81 mg/dL).

Because of immune thrombocytopenia (ITP), he received repeated courses of oral steroids associated with rituximab. This strategy remained ineffective: his global health status remained unstable with recurrent mucocutaneous bleeding and epistaxis. Two years later, he presented with lower limb weakness and right partial motor seizures. Multiple brain MRIs revealed recurrent brain and spinal cord lesions (figure 1C). A gene panel analysis identified a heterozygous deletion (c.109+1093_558-513del) in the *CTLA4* gene.

He was then treated with abatacept (CTLA4-Ig), and his general condition progressively improved (complete remission of ITP and bleedings, along with a dramatic reduction in the volume of lymph nodes and liver (figure 1B). Subsequent brain MRI follow-up did not reveal any additional lesions (42 months' follow-up, image not shown).

Patient 2

Patient 1's sister (figure 1A, III8), who carried the same mutation, had unexplained brain lesions (figure 1D) identified in the context of headaches and transient hemianopsia treated with steroid pulse when she was aged 13 years. From age 2 years, she had been having severe lymphoproliferation, autoimmune manifestations, and multiple infections (table). She was thus diagnosed with combined immunodeficiency. However, for years, multiple immunosuppressive therapies including cyclophosphamide, rituximab, and immunoglobulin supplementation remained ineffective on her global health status. She died at age 16 years due to severe pneumococcal sepsis.

It should be noted that several of their relatives (figure 1A) including their brother and their unaffected father carried the same mutation.

Patient 3

A 54-year-old woman presented with walking difficulties associated with bilateral axonal optic neuropathy and bladder urgency. Although optic neuropathy progressively worsened, resulting in severe bilateral vision loss (from 160/200 and 140/200 to 30/200 bilaterally within 4 years), she progressively developed severe upper limb dysmetria and speech/swallowing disorders. Clinical examination showed spastic tetraparesis with unsteadiness, marked dysmetria, and head tremor. Cognitive testing was normal. A brain MRI performed at age 55 years identified subtle white matter and deep basal ganglia FLAIR hyperintensities, as well as cerebellar atrophy and optic atrophy (figure 2, A–D). Another MRI performed 5 years later disclosed a dramatic increase in FLAIR hyperintensities (figure 2, E–H). A complete workup looking for autoimmune, paraneoplastic, and infectious causes was negative. CSF analysis disclosed normal cell count and protein level with 4 CSF-specific oligoclonal bands. A mini-exome analysis identified a heterozygous stop codon within exon 2 of the *CTLA4* gene (c.151C>T; p.Arg51*).

The patient's previous family history was unremarkable. However, her own medical history revealed recurrent infections going back to when she was aged 40 years. A complete immunologic workup identified both IgA and IgG deficiency. She thus began monthly supplementation with IV immunoglobulin at age 50 years. This treatment regimen contributed to reduce the frequency of ear, nose, and throat as well as lung infections. Treatment with abatacept was initiated in August 2019.

Discussion

We report a complete description of the clinical and radiologic characteristics of neurologic involvement in the context of *CTLA4* gene haploinsufficiency. These features may occur from the onset of adolescence to late adulthood, either as infiltrating lymphoproliferative lesions or, more surprisingly, as progressive symptoms mimicking genetic neurodegenerative disorders, including progressive cerebellar ataxia and inherited leukoencephalopathies.[5]

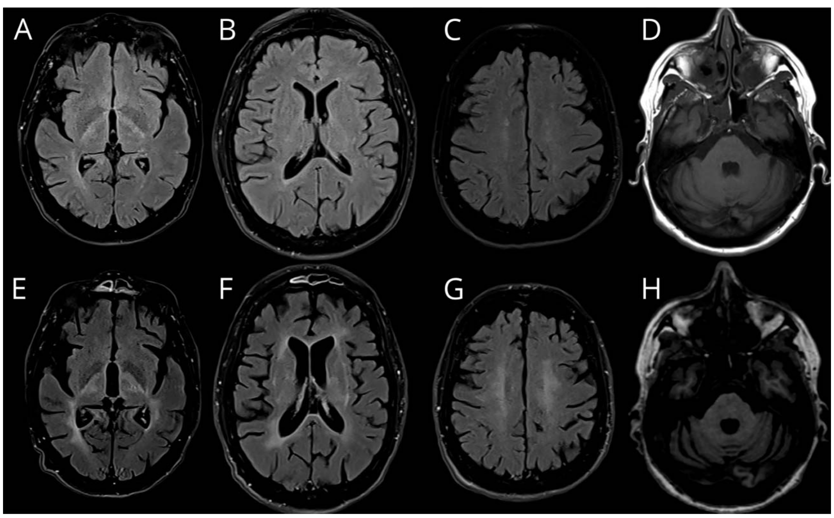
Although CNS lesions have been described in almost 30% of patients with CTLA4 insufficiency, the neurologic spectrum seems to be broad, ranging mainly from autoimmune encephalitis and perivascular lymphocytic infiltration to inflammatory disorders, optic neuritis, and lymphoproliferative disorders with CNS infiltration.[3–7] Whether our patients' neurologic involvement, notably in patients 1 and 2, is caused by an autoimmune reaction or by a lymphoproliferative process is not clear. Unfortunately, despite the presence of subtle inflammatory CSF changes in patients 1 and 3, it is difficult to favor 1 mechanism, notably in the absence of EBV PCR and pathologic analysis.

Surprisingly, the clinicoradiologic phenotype seen in patient 3 was clearly different from previously published cases, as it was mainly characterized by (1) the progressive development of cerebellar ataxia and visual loss and (2) the presence of bilateral and symmetrical white matter changes, reminiscent of those seen in inherited leukodystrophies/leukoencephalopathies.[8,9] Although we cannot exclude the highly unlikely presence of 2 very rare genetic disorders in a same patient, multiple panel gene excluded the main known causes of inherited leukoencephalopathy, cerebellar ataxia, and mitochondrial diseases.

Although our patients had been diagnosed with combined immunodeficiency years before neurologic manifestations, it is noticeable that in patient 3, the onset of symptoms occurred in her 40s and only preceded neurologic involvement by 5 years. Moreover, it has been suggested that neurologic symptoms can reveal CTLA4 insufficiency in almost 5% of patients.[5,7] Consequently, irrespective of the neurologic phenotype (which can be extremely varied), CTLA4 insufficiency and other inherited immunodeficiency should be suspected, whatever the temporal relationship between the onset of systemic and neurologic symptoms. A complete examination and a blood immunologic workup, including a complete lymphocyte phenotyping and IgG subclass measurement, should thus be performed to gather evidence in favor of a potential inherited immunodeficiency.

In addition, the search for CTLA4 insufficiency is strongly justified by the possibility of using targeted therapy,

Figure 2 Patient 3's MRI findings



MRI revealed diffuse white matter and basal ganglia FLAIR hyperintensities (A–C and E–G) and cerebellar atrophy (D and H), which progressively worsened from age 52 years (upper panel) to 56 years (lower panel).

i.e., abatacept. Patients 1 and 3 were treated with abatacept, as recently proposed.[5,10] In patient 1, this resulted in a marked improvement of systemic and biological conditions associated with stability of the CNS MRI lesion load. Unfortunately, patient 3's follow-up was too short to identify any meaningful neurologic improvement, but the IV immunoglobulin supplementation could be stopped shortly after the beginning of abatacept treatment.

Our cases suggest that the range of neurologic manifestations associated with CTLA4 insufficiency may be wide and not merely restricted to lymphoproliferative/autoimmune systemic manifestations. Any unexplained neurologic condition consistent with those presented herein, notably in the context of lymphoproliferative disorder, autoimmunity, or immunodeficiency, should benefit from extended workup to identify inherited combined immunodeficiency that can benefit from today's available potentially effective therapy.

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Clarisse Carra-Dallière, MD	Montpellier University Hospital	Data collection and drafting and reviewing of the manuscript
Claire Lozano, MD	Montpellier University Hospital	Data collection and drafting and reviewing of the manuscript
Pierre Portales, MD	Montpellier University Hospital	Data collection and drafting and reviewing of the manuscript
Thierry Vincent, MD, PhD	Montpellier University Hospital	Drafting and reviewing of the manuscript
Jean François Viallard, MD, PhD	Montpellier University Hospital	Drafting and reviewing of the manuscript
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Pierre Labauge, MD, PhD	Montpellier University Hospital	Data collection and drafting and reviewing of the manuscript
Philippe Guilpain, MD, PhD	Montpellier University Hospital	Data collection and drafting and reviewing of the manuscript

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