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Management of Autoimmune Encephalitis in a 7-Year-Old Child With CTLA-4 Haploinsufficiency and AMPA Receptor Antibodies

A Case Report

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Abstract

Objectives

We report on the therapeutic management of early-onset severe neurologic symptoms in cytotoxic T lymphocyte antigen-4 haploinsufficiency (CTLA-4h) and the presence of antibodies to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) as an important finding.

Methods

This is a case report from a Dutch academic hospital. Repeated clinical examinations, repeated brain MRI and extended diagnostics on serum and CSF were performed. We used the CARE checklist.

Results

A 7-year-old boy was diagnosed with CTLA-4h based on family screening. On diagnosis, he had mild chronic diarrhea and autism spectrum disorder, but no abnormalities in extensive laboratory screening. Six months later, he presented with sudden-onset autoimmune encephalitis. Repeated brain MRI revealed no abnormalities, but immunohistochemistry analysis on serum and CSF showed the presence of AMPAR antibodies. Treatment was initially focused on immunomodulation and targeted CTLA-4 replacement therapy. Because of the persistent fluctuating cerebellar and neuropsychiatric symptoms and the potential clinical significance of the AMPAR antibodies, treatment was intensified with repetition of first-line immunomodulation and rituximab. This combined therapy resulted in sustained clinical improvement and served as a bridge to curative hematopoietic stem cell transplantation.

Discussion

This case illustrates the rare early onset of autoimmune encephalitis and presence of AMPAR antibodies in CTLA-4h. Targeted CTLA-4 replacement therapy resulted in a partial response. However, awaiting its optimal therapeutic effect, refractory CNS symptoms required intensification of immunomodulation. The identification of AMPAR antibodies guided our treatment decisions.

Classification of Evidence

This provides Class IV evidence. It is a single observational study without controls.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Introduction

Cytotoxic T lymphocyte antigen-4 haploinsufficiency (CTLA-4h) is an immune dysregulation syndrome, with impairment to downregulate immune activation of T cells. Survival of the autoreactive T cells results in autoimmunity and lymphoproliferation, as well as immunodeficiency due to disrupted T-cell and B-cell homeostasis.[1,2] There is a high phenotypic variability and incomplete penetrance even with identical genetic variants[1] possibly because of variation in the downstream sequelae of T-cell activation.[3] Most of the affected carriers have more than one organ system involved. The CNS can be affected in one-third although this is usually seen years after the onset of systemic autoimmune or infectious manifestations, accompanied by inflammatory CNS lesions on brain MRI.[2,4] A diagnostic delay of months to years before a genetic diagnosis can result in late initiation of targeted treatment and delayed improvement. Involvement of antineuronal antibodies in a patient with CTLA-4h and its possible significance for the clinical picture and treatment has not been previously reported. Here, we report on a child with a known familial CTLA-4h and sudden early-onset of severe neurologic symptoms, without brain MRI abnormalities. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibodies were present. Targeted CTLA-4h replacement therapy with abatacept was quickly initiated, but the addition of second-line immunomodulating treatment was necessary for clinical improvement.

Case

A 7-year-old boy was diagnosed with CTLA-4h after familial screening because of affected relatives with a new pathogenic variant [c.231_297delinsA, p.(Gln80_Ser101del)]. Pathogenicity was confirmed using functional assays as described by Hou et al.[5] In affected relatives, but not controls, memory regulatory T cells had low relative CTLA-4 expression compared with expression in naïve conventional T cells. The functional defect was established both before and after T-cell stimulation.

His medical history consisted of mild chronic diarrhea unaffecting his growth and autism spectrum disorder. At first presentation, laboratory examination revealed no signs of systemic inflammation, celiac disease antibody screening was negative, and fecal calprotectin was mildly elevated. Immunologic screening showed normal white blood cell count, lymphocyte subsets, and immunoglobulin levels. Six months later, he presented at the emergency department with vomiting, headache, intermittent diplopia, and subsequently developed a gait disorder with frequent falls. There were no signs of encephalopathy or epilepsy. He did not have a fever or a history of recent illness. However, his diarrhea had worsened with increase in fecal calprotectin, resulting in failure to thrive. Neurologic examination revealed a significant cerebellar gait ataxia, saccadic intrusions, and nystagmus but was otherwise unremarkable.

Blood tests for immunologic screening and inflammatory markers were normal (Table). Brain MRI including contrast-enhanced sequences showed no abnormalities. CSF pressure was normal, and CSF analysis showed a lymphocytic pleocytosis. Routine microbiological testing was negative (Table). Cytology and immunophenotyping were not indicative for any malignancy. The provisional diagnosis entailed a neuroinflammatory disorder within the context of the underlying CTLA-4h. During subsequent diagnostic evaluation, immunohistochemistry analysis adding serum and CSF to rat brain revealed an intense neuropil staining. Extensive additional cell-based assays (CBA) for extracellular neural targets showed antibodies against AMPAR in both serum and CSF (Table). A recent chest CT, performed to screen for pulmonary involvement in CTLA-4h, showed no evidence of paraneoplastic origin of AMPAR antibodies.

Initial treatment consisted of IV methylprednisolone pulses (IVMP) followed by oral prednisolone and IV immunoglobulins (IVIG) (Figure). The neurologic symptoms stabilized, and his diarrhea and calprotectin levels improved. CTLA-4 replacement therapy with abatacept was introduced consisting of 3 IV cycles every 2 weeks followed by weekly subcutaneous administration (Figure). Neurologic symptoms gradually improved while tapering oral prednisolone. However, severe anxiety and insomnia emerged, prompting renewed immunomodulatory IVIG treatment in 4-weekly repeated cycles. In addition, 2 weeks after prednisolone was reduced below 1 mg/kg/day, cerebellar symptoms recurred. Repeated brain MRI was unremarkable, and CSF analysis demonstrated near-normalized cell counts although AMPAR antibodies were still detectable in both CSF and serum (Table). Treatment was intensified with IV rituximab and IVMP was repeated followed by slow tapering of oral prednisolone. Within 4 weeks, there was significant clinical improvement of the cerebellar symptoms. Mood swings and insomnia recovered slowly. Nine months after start of initial treatment, he was admitted in stable condition for allogeneic hematopoietic stem cell transplantation (HSCT) aiming definitive treatment of his CTLA-4h. The effective combination of weekly subcutaneous abatacept and monthly IVIG with low-dose corticosteroids was continued until admission for HSCT. Currently 1 year post-HSCT, he presents mixed chimerism but is in good clinical condition with no enteropathy or CNS symptoms except for his preexistent autism spectrum disorder. Serum AMPAR antibodies remain undetectable using CBA.

Discussion

We report on the treatment of a child with rare early-onset CTLA-4h–related autoimmune encephalitis and presence of AMPAR antibodies. Treatment succeeded when combining CTLA-4 replacement therapy with intensified immunomodulation consisting of (methyl)prednisolone, IVIGs, and rituximab.

In general, therapeutic options for CTLA-4h focus on controlling T-lymphocyte activation by inhibiting the underlying hyperactive signaling. This includes immunomodulatory or

Table Serum and CSF Analysis at Presentation With CNS Symptoms and During Recurrence of Cerebellar Symptoms

	At presentation	At treatment-related fluctuation
Serum		
C-reactive protein [ref 0–10 mg/L]	<0.6 mg/L	<0.6 mg/L
Erythrocyte sedimentation rate	8 mm/h	—
Immunoglobulin levels: IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgM	Normal	—
Leukocytes and differential count	Normal	—
Lymphocyte subsets: T cells ($CD3^+$, $CD4^+$, $CD8^+$ (naive, central memory, effector memory), CD4/CD8 ratio, B-cells (transitional, naive, natural effector, memory), natural killer cells	Normal	—
Anti-GAD65	Negative	—
Anti-CASPR2	Negative	—
Anti-AMPAR[a]	Positive	Positive
Anti-glycine-R	Negative	—
Anti-DPPX	Negative	—
Anti-MOG	Negative	—
Anti-AQP4	Negative	—
CSF		
Leukocytes ($\times 10^6$/L)	90	3
Total protein (g/L)	1.51	0.21
Erythrocytes ($\times 10^6$/L)	9000	<500
Glucose (mmol/L)	3.4	3.6
IgG index	1.13	0.57
Protein electrophoresis	—	1 Ig band
Microbiological testing: (an)aerobic culture. PCR neurotropic viruses (herpes simplex type 1 and 2, varicella zoster, cytomegalo, Epstein-Barr, adenovirus, enterovirus, parechovirus)	Negative	Negative
Anti-NMDAR	Negative	Negative
Anti-AMPAR[a]	Positive	Positive
Anti-GABAb-R	Negative	Negative
Anti-GFAP	Negative	—

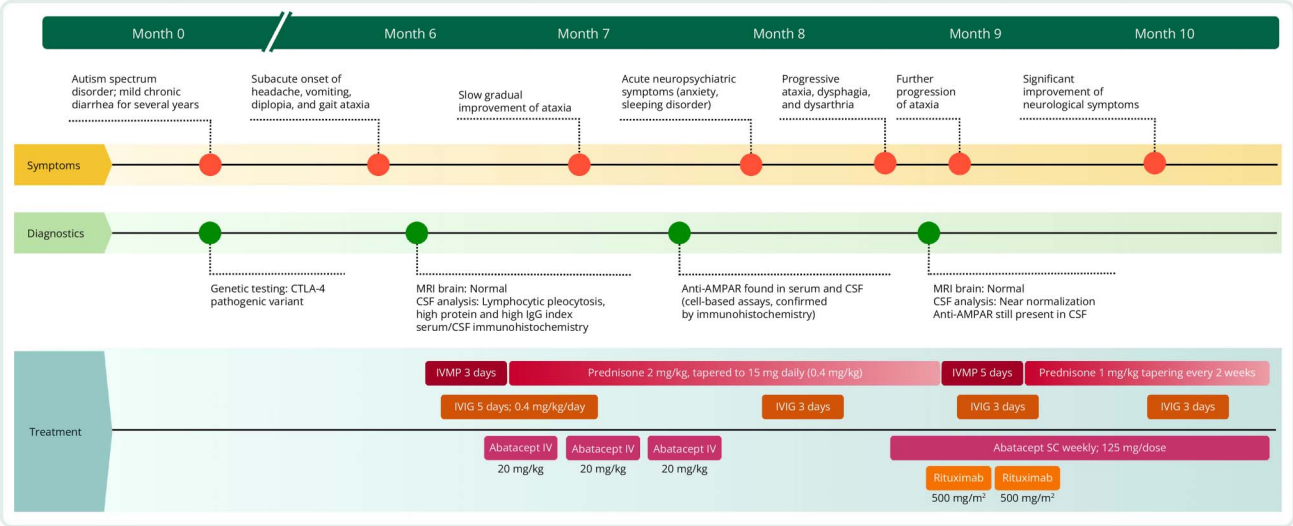
Abbreviations: Anti-AMPAR = anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Anti-AQP4 = anti-aquaporine-4; Anti-CASPR2 = anti-contactin–associated protein-like 2; Anti-DPXX = anti-dipeptidyl-peptidase-like protein 6; Anti-GABAb-R = anti-gamma-aminobutyric acid-B receptor; Anti-GAD65 = anti-glutamic acid decarboxylase 65; Anti-GAFP = anti-glial fibrillary acidic protein; Anti-glycine-R = anti-glycine receptor; Anti-MOG = anti-myelin oligodendrocyte glycoprotein; Anti-NMDAR = anti-N-methyl-D-aspartate receptor; Ig = immunoglobulin.
[a] Testing involved in house live cell-based assay, in house fixed cell-based assay and confirmation by rat brain immunohistochemistry.

immunosuppressive therapies as well as targeted therapy consisting of either CTLA-4 immunoglobulin fusion protein (abatacept, belatacept) or a mechanistic target of rapamycin inhibitor like Sirolimus.[1,2] According to expert opinion, CTLA-4h–related severe neurologic symptoms may require individualized treatment.[2]

In the small number of previously reported cases of CTLA-4h–related CNS involvement, the majority had T2-hyperintense MRI brain lesions.[4,6-10] Only 3 cases had abnormal CSF analysis but normal brain MRI,[8,9] similar to our case. Notably, in the majority, the genetic diagnosis was not known at onset of symptoms. As a result, the subsequent treatment initially did not prioritize CTLA-4 replacement therapy and only after its addition partial or even complete recovery has been reported.[4,6-11] In our case, despite the immediate initiation of abatacept, additional treatment was still required.

The identification of antibodies aimed against extracellular (membrane-bound) targets has not been reported before in CTLA-4h. Although we cannot exclude that AMPAR

Figure Overview of Clinical Phenotype and Therapeutic Management



antibodies represent an epiphenomenon in our case, several clues suggest that they caused the symptoms. AMPAR antibodies are directly pathogenic[12] and anti-AMPAR encephalitis can occur in children, not necessarily involving seizures or abnormal brain MRI.[13,14] The prominent anxiety and insomnia in our case are likely related to limbic encephalitis symptoms, although aggravation of these symptoms secondary to long-term systemic corticosteroid use cannot be excluded. Furthermore, AMPAR antibodies may also account for the cerebellar symptoms considering that ataxia is present in up to 24% of patients with anti-AMPAR encephalitis.[13]

First-line treatment in our patient focused on autoimmune encephalitis, adding targeted treatment with abatacept. The fluctuating neurologic symptoms while tapering steroids could be attributed to the long-term presence of AMPAR antibodies or to the delayed effect of abatacept (which may take 3 to 6 months). We therefore repeated first-line treatment and initiated second-line treatment with rituximab.[13,15] This resulted in clinical improvement. It remains unclear whether rituximab or abatacept combined with reintroducing methylprednisolone and structural IVIG administration caused this improvement. However, earlier administration of rituximab could have been useful as a steroid-sparing agent. Therefore, we emphasize the need of combined therapy in CTLA-4h–related autoimmune encephalitis with the presence of AMPAR antibodies. Based on his young age and multiorgan disease, he underwent an allogeneic HSCT aiming at life-long cure.[2]

We here show CNS symptoms in CTLA-4h occurring as an early manifestation of disease in a child. Specific antineuronal antibodies like AMPAR antibodies may be associated to this early onset as well as the refractory course. In our case, individualized treatment combining CTLA-4 replacement therapy with high dose steroids, IVIGs, and second-line treatment with rituximab resulted in clinical improvement.

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Disclosure

M.J. Titulaer has received research funds for serving on a scientific advisory board of Horizon Therapeutics and UCB; M.J. Titulaer has filed a patent, on behalf of Erasmus MC, for methods for typing neurologic disorders and cancer, and devices for use therein, and has received research funds for consultation at Guidepoint Global LLC and unrestricted research grants from CSL Behring and Euroimmun AG; M.J. Titulaer is supported by an E-RARE 3 grant (UltraAIE), the Dutch Epilepsy Foundation (NEF 19-08) and Dioraphte (2001 0403) M.S.W. Quaak, M.S.J. Buijze, V.J.M. Verhoeven, C. Vermont, E.P. Buddingh, M. Heredia, J.N. Samsom, A.M.C. van Rossum, S. Kamphuis, R.F. Neuteboom report no disclosures relevant to the manuscript. Go to Neurology.org/NN for full disclosures.

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Appendix *(continued)*

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