Rapidly Progressive Cerebellar Hemiataxia with High Levels of GAD65 Reactive Antibodies

Wiels, Wietse; Guisset, Francois; Vandervorst, Fenne; Peeters, Ilse; Seynaeve, Laura; Costa, Olivier; Flamez, Anja; De Keyser, Jacques

Published in:
Movement Disorders Clinical Practice

DOI:
10.1002/mdc3.12504

Publication date:
2017

Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Rapidly Progressive Cerebellar Hemiataxia with High Levels of GAD65 Reactive Antibodies

Wietse Wiels, MD,[1,*] Francois Guisset, MD,[1] Fenne Vandervorst, MD,[1] Ilse Peeters, MD,[1] Laura Seynaeve, MD,[1] Olivier Costa, MD, PhD,[2] Anja Flamez, MD,[1] Jacques De Keyser, MD, PhD[1,3]

Introduction

Clinicians should consider glutamic acid decarboxylase (GAD)-antibody–associated disease in patients who present with nonstructural cerebellar hemiataxia, because these patients may benefit from early immune therapy.[1–3]

Case Report

A 68-year-old woman presented to our hospital because of dizziness, clumsiness, and gait deviation, all of which had progressed over a period of 2 months. Her medical history was notable for noninsulin-dependent diabetes, arterial hypertension, and hepatitis C infection, the latter having been treated successfully with a 16-week regimen of ombitasvir, paritaprevir, ritonavir, and ribavirin 2 years prior. Daily medications included amlodipine, bisoprolol, metformin, sitagliptin, and aspirin. She was well oriented, with intact speech and cognitive functioning. Cranial nerve examination was normal except for a mild gaze-evoked nystagmus. Strength and muscle tone were normal. She had a mildly ataxic heel-to-shin test on the right. There were no sensory deficits. Deep tendon reflexes were normal in the upper limbs and reduced in the lower limbs, with flexor plantar responses. Shoulder mobilization on the right was limited and painful. Magnetic resonance images of the brain and spinal cord were unremarkable. Routine blood tests were normal apart from an elevated erythrocyte sedimentation rate of 51 mm/hour. A diagnosis of adhesive shoulder capsulitis was made, and the patient was referred to physical therapy.

Four weeks later, however, the patient was readmitted after further deterioration. Examination revealed severe right-sided dysmetria on both the finger-to-nose test and the heel-to-shin test; dysdiadochokinesis; a rebound phenomenon; and hypotonia. Cerebellar tests on the left side were completely normal. Gait testing demonstrated severe right-sided ataxia, necessitating full ambulatory support. The remainder of her general and neurologic examination was normal.

Repeat magnetic resonance imaging of the brain showed no abnormalities. Neurophysiological tests were unremarkable except for an increased latency of the left P100 visual-evoked potential, which was attributed to moderately severe cataract. Routine blood tests, including vitamin status as well as celiac, thyroid, and antinuclear antibodies, were normal. Whole-body positron emission-computed tomography did not show any hypermetabolic lesions. Mammography and transvaginal ultrasound were normal. Cerebrospinal fluid analysis demonstrated normal cell count, protein, and glucose levels. There were 5 oligoclonal bands, 3 of which were also found in serum. Results from an antineuronal antibody panel as well as immunofluorescence on simian cerebellar slices suggested the presence of autoantibodies (Fig. 1). Serum levels of GAD65-reactive antibodies were 677,619 U/mL (4000 times the upper limit of normal), and cerebrospinal fluid levels were 7380 U/mL. Other neuronal autoantibodies currently known to be associated with cerebellar ataxia (e.g. anti-Yo, anti-Hu, anti-Tr, antivoltage-gated calcium channel [anti-VGCC], antiglutamate receptor-like molecule δ2 [anti-GluRδ2], . . .) were negative.

The patient was treated with intravenous methylprednisolone 500 mg daily for 7 days and experienced a dramatic improvement (Table 1, Video S1). Because of steroid-related issues with glycemic control, she was further treated with 2 sessions of

[1]Department of Neurology, UZ Brussel and Centre for Neurosciences (C4N), Vrije Universiteit Brussel, Brussels, Belgium; [2]Department of Clinical Biology, UZ Brussel and Diabetes Research Centre, Vrije Universiteit Brussel, Brussels, Belgium; [3]Department of Neurology, University Groningen, University Medical Centre Groningen, Groningen, the Netherlands

***Correspondence to:** Dr. Wietse Wiels, UZ Brussel-Brussels University Hospital, Laarbeeklaan 101, 1090 Jette, Brussels, Belgium; E-mail: wwiels@vub.ac.be
Keywords: cerebellum, glutamic acid decarboxylase (GAD)-antibody–associated disease, GAD65, GADA, hemiataxia, immune-mediated cerebellar ataxia.
Supporting information may be found in the online version of this article.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 23 February 2017; revised 3 April 2017; accepted 17 April 2017.
Published online 1 June 2017 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12504

doi:10.1002/mdc3.12504

intravenous immunoglobulins for 5 days, after which azathioprine maintenance therapy was initiated.

Discussion

GAD-antibody–associated autoimmunity is a known cause of several neurologic syndromes, including stiff-person syndrome, limbic encephalitis, and cerebellar ataxia.[3] Although lateralized findings are not without precedent in immune-mediated disorders, such as Rasmussen's encephalitis[4] and leucine-rich, glioma inactivated 1 (LGI1)-associated faciobrachial dystonic seizures, it remains peculiar that antibodies targeting a ubiquitous protein should produce strictly unilateral findings. To our knowledge, only 1 case of GAD-antibody–associated hemiataxia has been published previously.[5]

Our patient did not show other characteristics of GAD65-spectrum patients, such as organ-specific autoimmunity.[1,3,4] However, she did react quite well to corticosteroids and intravenous immunoglobulins, in accordance with what has been reported in case series.[1,2] Compared with antibodies to other classical intracellular cytoplasmic targets, which usually were considered harbingers of a poor prognosis in immune-mediated neurologic disorders,[2] GAD-antibody–associated disease often has a relatively good outcome and response to treatment. This observation has led some authors to suggest that an unidentified cell-surface type antibody (or another mechanism entirely) might be the actual pathogenic suspect, although this is a controversial issue.[1,3] This case provides further evidence that early immune therapy may benefit patients suffering from immune-mediated ataxia.[1]

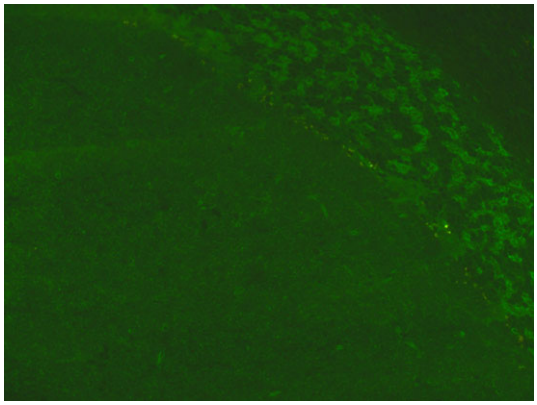

Figure 1 Antibody fluorescence using a 1/10 dilution of the patients' serum. The image shows spotted coloration of the stratum granulosum in simian cerebellar tissue. Courtesy of Euroimmun AG.

TABLE 1 Physical test scores before and after treatment

Test	Before treatment	After IV MP	After IV Ig
Frenchay arm test	2/5: Lifting 2 objects, tremulously	5/5	5/5
Timed up and go test, s	55	27	15
Nine-hole peg test, s			
Left	24	26	23
Right	49	40	37
Scale for the Assessment and Rating of Ataxia, points	20.5	9	9

IV, intravenous; MP, methylprednisolone; Ig, immunoglobulin.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

W.W.: 1B, 1C, 3A, 3B
F.G.: 1B, 3B
I.P.: 1A
F.V.: 1A
L.S.: 3B
O.C.: 1B, 1C
A.F.: 1A, 3B
J.D.K.: 1B, 3B

Acknowledgements

We thank the patient and her family for cooperating in the publication of this material and providing written informed consent. CSL Behring provided the intravenous immunoglobulins through their compassionate use program.

Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflict of Interest: The authors report no sources of funding and no conflicts of interest relevant to this work.

Financial Disclosures for the previous 12 months: Laura Seynaeve reports grant 09050 from IWT-TMB. Olivier Costa reports an IWT DS grant. The remaining authors report no sources of funding and no conflicts of interest.

References

1. Ariño H, Gresa-Arribas N, Blanco Y, et al. Cerebellar ataxia and glutamic acid decarboxylase antibodies: immunologic profile and long-term effect of immunotherapy. *JAMA Neurol* 2014;71:1009–1016.
2. Mitoma H, Hadjivassiliou M, Honnorat J. Guidelines for treatment of immune-mediated cerebellar ataxias [serial online]. *Cerebellum Ataxias* 2015;2:14.
3. Saiz A, Blanco Y, Sabater L, et al. Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. *Brain* 2008;131(pt 10):2553–2563.

doi:10.1002/mdc3.12504

4. Varadkar S, Bien CG, Kruse CA, et al. Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances. *Lancet Neurol* 2014;13:195–205.

5. Schreck KC, Orthmann-Murphy JL, Newsome SD. Clinical reasoning: a 70-year-old woman with acute-onset weakness and progressive hemiataxia. *Neurology* 2016;87:e264–e268.

Supporting Information

A video accompanying this article is available in the supporting information here.

Video S1. Hemiataxia is observed before and after treatment.

doi:10.1002/mdc3.12504