

# Autoimmune episodic ataxia in patients with anti-CASPR2 antibody-associated encephalitis

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## ABSTRACT

**Objective:** To report paroxysmal episodes of cerebellar ataxia in a patient with anti-contactin-associated protein-like 2 (CASPR2) antibody-related autoimmune encephalitis and to search for similar paroxysmal ataxia in a cohort of patients with anti-CASPR2 antibody-associated autoimmune encephalitis.

**Methods:** We report a patient with paroxysmal episodes of cerebellar ataxia observed during autoimmune encephalitis with anti-CASPR2 antibodies. In addition, clinical analysis was performed in a retrospective cohort of 37 patients with anti-CASPR2 antibodies to search for transient episodes of ataxia. Paroxysmal symptoms were further specified from the referral physicians, the patients, or their relatives.

**Results:** A 61-year-old man with limbic encephalitis and anti-CASPR2 antibodies developed stereotyped paroxysmal episodes of cerebellar ataxia, including gait imbalance, dysarthria, and dysmetria, 1 month after the onset of the encephalitis. The ataxic episodes were specifically triggered by orthostatism and emotions. Both limbic symptoms and transient ataxic episodes resolved after treatment with steroids and IV cyclophosphamide. Among 37 other patients with anti-CASPR2 antibodies, we identified 5 additional cases with similar paroxysmal ataxic episodes that included gait imbalance (5 cases), slurred speech (3 cases), limb dysmetria (3 cases), and nystagmus (1 case). All had concomitant limbic encephalitis. Paroxysmal ataxia was not observed in patients with neuromyotonia or Morvan syndrome. Triggering factors (orthostatism or anger) were reported in 4 patients. Episodes resolved with immunomodulatory treatments in 4 patients and spontaneously in 1 case.

**Conclusions:** Paroxysmal cerebellar ataxia must be added to the spectrum of the anti-CASPR2 antibody syndrome. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e371; doi: 10.1212/NXI.0000000000000371

## GLOSSARY

EA = episodic ataxia.

Episodic ataxias (EAs) are a group of hereditary channelopathies whose common feature is the occurrence of paroxysmal episodes of cerebellar ataxia.<sup>1</sup> Ataxic episodes usually last a few minutes to a few days and can be triggered by emotions, abrupt movements, exercise, or fever. Depending on which ion channel gene is mutated, additional symptoms, such as neuromyotonia or epilepsy, can occur.<sup>2</sup> Conversely, paroxysmal symptoms are rare in patients with antineuronal antibody-associated neurologic disorders, and EAs have not yet been reported in such cases. In this study, we report a patient with paroxysmal episodes of ataxia developed during autoimmune encephalitis with anti-CASPR2 antibodies. To assess the relevance of our case, we retrospectively

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From the Centre National de Référence pour les Syndromes Neurologiques Paraneoplasiques (B.J., L.T., V.D., V.R., G.P., F.D., D.P., J.-C.A., J.-Y.D., J.H.), Service de Neuro-Réanimation (F.G.), Hôpital Neurologique, Hospices Civils de Lyon, Bron; Institut NeuroMyoGene INSERM U1217/CNRS UMR 5310 (B.J., F.G., L.T., M.S.-M., V.D., V.R., G.P., F.D., J.H.), University of Lyon—Université Claude Bernard Lyon 1; Service de Neurologie (P.C., J.-C.A.), Hôpital Bellevue, Centre Hospitalier Universitaire de Saint-Étienne; and Département de Neurologie (D.P., J.-Y.D.), Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique—Hôpitaux de Paris, France.

Funding information and disclosures are provided at the end of the article. Go to [Neurology.org/nn](https://www.neurology.org/nn) for full disclosure forms. The Article Processing Charge was funded by INSERM ADR05.

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searched for similar episodes of transient ataxia in a cohort of patients with anti-CASPR2 antibodies. Anti-CASPR2 antibody-related disorders encompass a wide range of neurologic autoimmune syndromes, including autoimmune encephalitis, neuromyotonia, and Morvan syndrome. A recent publication by Van Sonderen et al.<sup>3</sup> showed that up to 77% of the patients with such antibodies had at least 3 cumulated core neurologic symptoms, including encephalic signs, cerebellar symptoms, peripheral nerve hyperexcitability, dysautonomia, neuropathic pain, insomnia, and weight loss. Our study may contribute to further delineate anti-CASPR2 antibody-related clinical presentation.

**METHODS** We report a patient with autoimmune encephalitis, anti-CASPR2 antibodies, and paroxysmal cerebellar ataxia. Anti-CASPR2 antibodies were screened in serum and CSF as previously described.<sup>4</sup> Positivity of both an immunohisto-fluorescent assay on rat brain slices and a cell-based binding assay with HEK-293-transfected cells were needed to confirm the presence of anti-CASPR2 antibodies. A signed patient consent-to-disclose form has been obtained from the patient for a video recording of one of the episodes.

We also studied the clinical files of 37 patients with anti-CASPR2 antibodies, detected in their CSF or sera at the *Centre de Référence National pour les Syndromes Neurologiques Paraneoplastiques* (Lyon, France) between March 2009 and August 2016, to search for similar transient cerebellar symptoms. Thirty-three of those patients have been previously reported.<sup>4</sup> Written informed consent was obtained from all patients with approval of the Institutional Review Board of the Hospices Civils de Lyon. We selected all patients who had been reported by their referral physicians to have symptoms that were both transient and suggestive of cerebellar impairment, i.e., gait imbalance, slurred speech, or limb dysmetria. Further information was collected by telephone from the referral physicians, and, when possible, from the patients themselves or their relatives.

**RESULTS** **Index case.** A 61-year-old man was hospitalized for evaluation after a tonic-clonic generalized seizure. He was still active as a corporate executive, and his medical history included high blood pressure, diabetes, myocardial infarction, and a smoking habit. No prodromal or postictal symptom was reported, but the patient reported slight memory impairment, difficulties to concentrate at work, unusual emotiveness, and anxiety over a few days before the seizure. The patient was treated with levetiracetam and clonazepam. However, the cognitive symptoms persisted and several partial temporal lobe seizures occurred. One month after the first seizure, the patient began to experience repeated episodes of slurred speech, gait ataxia, and slight dysmetria of the limbs (see video at [Neurology.org/nn](http://Neurology.org/nn)). These events occurred 3–4 times a day, were often triggered by emotions and

orthostatism, and lasted less than 1 minute. No cerebellar symptom was observed between the episodes. Levetiracetam was switched to lacosamide without any improvement of the symptoms.

Brain MRI was normal. EEG found an asymmetric temporal lobe slowing. CSF analysis found 16 white blood cells/mm<sup>3</sup>, a protein level of 65 mg/dL, and no oligoclonal band. Anti-CASPR2 antibodies were detected (end-point dilution using cell-binding-based assay, 1/40,960, in serum and 1/5,120 in CSF). Brain single-photon emission CT found bilateral frontotemporal hypoperfusion with normal perfusion of basal ganglia and cerebellum. Full-body CT was normal. Sequencing of the genes involved in EA types 1 and 2, *KCNA1* and *CACNA1A*, found that the patient carried a rare polymorphism in intron 39 of *CACNA1A* (c5843-14G>A).<sup>5,6</sup> *KCNA1* was normal. The patient was treated with 3 daily injections of 1 g methylprednisolone followed by 6 monthly pulses of 1 g cyclophosphamide. The frequency of the ataxia episodes decreased immediately; they had totally stopped 5 days after the end of the methylprednisolone pulses. The patient recovered all his cognitive abilities 2 weeks after the initiation of the treatment and had his last seizure 3 months after the first visit. At month 7 of follow-up, the patient remained asymptomatic and seizure free. At the peak of his disease, the patient had presented with only 2 core symptoms as defined by Van Sonderen et al.<sup>3</sup> (encephalic signs and cerebellar ataxia).

**Cohort study.** Among the cohort of 37 other patients with anti-CASPR2 antibodies (20 with encephalitis and 17 with neuromyotonia or Morvan syndrome), we retrospectively identified 5 patients with transient symptoms suggestive of cerebellar impairment. All the patients were men, with a median age of 60 years (range 57–69). Median follow-up (range) was 45.6 months (19.3–113.6). One patient had a history of surgically treated thyroid carcinoma. All these 5 patients had anti-CASPR2 antibodies in both serum and CSF and had a presentation of autoimmune encephalitis with prominent seizures and amnesia, as we previously reported.<sup>4</sup> Three patients also developed mild permanent cerebellar symptoms, concomitantly to (2 cases) or after (1 case) the onset of paroxysmal ataxia.

None of them exhibited neuromyotonia or Morvan syndrome. Two of the 5 patients had  $\geq 3$  core symptoms as defined in the study by Van Sonderen et al.<sup>3</sup> The transient episodes are described in the table. They were stereotyped and included, according to the cases, gait imbalance (5/5, 100%), slurred speech (3/5, 60%), limb dysmetria (3/5, 60%), and nystagmus (1/5, 20%).

**Table** Characteristics of the ataxia episodes in patients with autoimmune encephalitis and anti-CASPR2 antibodies

Age, y, sex	Follow-up, mo	Symptoms during the episodes	Triggering factors	Impact on daily activities	Duration of the episodes	Frequency at peak	Permanent cerebellar symptoms also present	Onset in relation to the onset of the limbic symptoms	Period during which paroxysmal ataxia occurred	Anti-CASPR2 ab titers		Treatments before resolution of the episodes
										Serum	CSF	
61, M	7	Gait imbalance, slurred speech, and limb dysmetria	Anxiety and orthostatism	No	<1 min	3-4/d	No	1 mo later	3 wk	1/40,960	1/1,520	Methylprednisolone, cyclophosphamide
62, M	114	Gait imbalance and slurred speech	None	No	A few minutes	2 episodes with an interval of 2 wk	No	10 mo later	2 wk	NA	1/320	None
57, M	51	Gait imbalance	Orthostatism	No	A few minutes to 2 h	3-5/wk	No	4 mo later	4 mo	1/10,240	1/640	Methylprednisolone, plasmapheresis
60, M	46	Gait imbalance, slurred speech, limb dysmetria, and neck stiffness	Orthostatism	Yes	A few minutes	2-3/d	Yes (gait imbalance and inferior limb dysmetria)	7 mo before	33 mo	1/10,240	1/10,240	Methylprednisolone
60, M	22	Gait imbalance, slurred speech, limb dysmetria, nystagmus, and neck stiffness	Orthostatism, anger	Yes	A few minutes	6-7/d	Yes (slight imbalance)	Concomitant	13 mo	1/10,240	1/10,240	Rituximab
69, M	19	Gait imbalance and limb dysmetria	Orthostatism	No	<1 min	<5/wk	Yes (slight imbalance)	17 mo later	2 mo	1/10,240	1/10,240	Prednisolone and IV immunoglobulin

Abbreviations: ab = antibodies; NA = not available. The first line refers to the index case.

Two patients (40%) reported concomitant sensations of neck stiffness. Myoclonic jerks were not observed in any of the patients. Of interest, the ataxia episodes preceded by 7 months the full development of the encephalitis in 1 patient. The apparition of the ataxia was not subsequent to a change of antiepileptic medication in any of the patients. The attacks were reported to last from a few minutes to 2 hours, according to the cases, with triggering factors identified in 4 patients (80%; orthostatism in 4 patients and anger in 1 patient). Ataxia episodes occurred during a mean period of 4 months (range, 0.5–32.5) and stopped after the initiation of an immunomodulatory treatment in 4 patients (steroids alone, steroids and plasmapheresis, steroids and IV immunoglobulin, or rituximab) and spontaneously in 1 case. Interictal, milder cerebellar symptoms were observed in 3/5 cases (60%). Interictal brain MRI was unremarkable in all patients; magnetic resonance spectroscopy was not performed during the episodes. We did not perform genetic studies in these 5 patients.

**DISCUSSION** In this study, we report stereotyped episodes of paroxysmal cerebellar ataxia in a patient with anti-CASPR2 antibody-related autoimmune encephalitis. We also retrospectively identified similar paroxysmal symptoms in 5 of 20 other patients with autoimmune encephalitis and anti-CASPR2 antibodies, suggesting that episodic cerebellar ataxia could be observed in up to 25% of such patients.

As they developed during the course of encephalitis and resolved after immunomodulating therapy in most of the patients, we can speculate an immune origin of these paroxysmal ataxias. Moreover, the association of gait imbalance, slurred speech, and limb dysmetria during these episodes was highly suggestive of cerebellar impairment; although because of the retrospective collection of the data, we cannot completely exclude that the alleged cerebellar symptoms were actually of another nature (e.g., orthostatic hypotension, seizures, or peri-ictal autonomic manifestations).

Paroxysmal neurologic symptoms have already been reported in autoimmune encephalitis. For instance, faciobrachial dystonic seizures are caused by the activation of the motor cortex in patients with anti-leucine-rich glioma1 (Lgi1) antibody-associated encephalitis.<sup>7</sup> Of interest, Lgi1 is a secreted protein that complexes with CASPR2 and the potassium channel K<sub>v</sub>1.1.<sup>5,8</sup> More recently, orthostatic myoclonus has been observed in a patient with anti-CASPR2 antibodies.<sup>9</sup> Although permanent ataxia without remissions is a well-described feature of anti-CASPR2 antibody-associated encephalitis, to our knowledge, EA has never been reported before in patients with

autoimmune encephalitis, including for instance patients with anti-Lgi1 encephalitis.<sup>4,3,10,11</sup>

Anti-CASPR2 antibodies associate with various neurologic disorders, including limbic encephalitis, neuromyotonia, and Morvan syndrome.<sup>3,4,12–14</sup> In a recent published cohort of 38 anti-CASPR2 antibody-positive patients, 77% of the cases had  $\geq 3$  core symptoms (encephalic signs, cerebellar symptoms, peripheral nerve hyperexcitability, dysautonomia, neuropathic pain, insomnia, and weight loss).<sup>3</sup> In our previously published cohort of 33 patients with anti-CASPR2 antibodies, only 16/33 (48%) of the patients presented with  $\geq 3$  of those core symptoms.<sup>4</sup> However, patients with limbic encephalitis were overrepresented and we found a greater number of patients with  $\geq 3$  core symptoms in the group of patients diagnosed with neuromyotonia or Morvan syndrome (13/15, 87%) than in the group of patients diagnosed with limbic encephalitis (3/18, 17%). Only 2/6 (33%) of our patients with paroxysmal ataxia had  $\geq 3$  core symptoms, which reflects that this paroxysmal syndrome is mostly associated with limbic encephalitis rather than neuromyotonia or Morvan syndrome.

The resemblance of the patients' paroxysmal ataxia with manifestations observed in hereditary channelopathies such as EA is striking. Of interest, neuromyotonia can be observed in patients with EA type 1 and anti-CASPR2 antibodies, suggesting similar ion channel dysfunctions in both diseases. EA type 1 is due to mutations of *KCNA1*, a gene coding for the voltage-gated potassium channel  $K_V1.1$ .<sup>5,13</sup> The clustering of  $K_V1.1$  at the nodes of Ranvier depends on CASPR2, and electrophysiologic experiments have suggested an impairment of voltage-gated potassium channels in autoimmune neuromyotonia, implying that anti-CASPR2 antibodies might indirectly alter the functions of  $K_V1.1$  at the nodes of Ranvier.<sup>15,16</sup> However, previous studies have failed to demonstrate a role of CASPR2 in  $K_V1.1$  clustering at the synaptic level, and the exact role of anti-CASPR2 antibodies in the CNS is unknown.<sup>16,17</sup> Nevertheless, our observation supports the hypothesis of immune-mediated ion channel dysfunction in anti-CASPR2 antibody syndromes. The polymorphism of *CACNA1A* in the index patient is interesting because this gene codes for the  $Ca_V2.1$  subunit of the P/Q type voltage-gated calcium channel that is mutated in patients with EA type 2.<sup>6</sup> We have no data about the significance of this polymorphism, whose overall frequency in the general population is estimated at less than 1/1,000. However, we can hypothesize that it may provoke a partial impairment of  $Ca_V2.1$ .<sup>6</sup> We can thus speculate that in the case, this polymorphism of *CACNA1A* may have led to the failure of compensatory mechanisms dependent on  $Ca_V2.1$  and necessary

to counterbalance the effects of anti-CASPR2 antibodies. Therefore, this polymorphism may have favored the development of episodic cerebellar symptoms in the patient.

Overall, our findings suggest that transient cerebellar ataxia should be added to the spectrum of anti-CASPR2 antibody-related symptoms. Such paroxysmal symptoms are similar to the symptoms of hereditary channelopathies, suggesting that ion channel dysfunction is involved in the pathogenesis of anti-CASPR2 antibody syndromes.

## AUTHOR CONTRIBUTIONS

Dr. Joubert: study concept and design; acquisition of data; and analysis and interpretation. Dr. Gobert: acquisition of data and critical revision of the manuscript for important intellectual content. Dr. Thomas and Ms. Saint-Martin: acquisition of data. Dr. Desestret: critical revision of the manuscript for important intellectual content. Dr. Convers, Dr. Rogemond, and Ms. Picard: acquisition of data. Prof. Ducray, Dr. Psimaras, Prof. Antoine, and Prof. Delattre: critical revision of the manuscript for important intellectual content. Dr. Honnorat: study supervision; acquisition of data; study concept and design; and critical revision of the manuscript for important intellectual content.

## ACKNOWLEDGMENT

The authors thank Dr. Cécile Marchal, Dr. Philippe Kassiotis, Dr. Jacques Testaud, Dr. Lejla Koric, and Dr. Isabelle Lambert, who provided CSF, serum samples, and clinical data for the study.

## STUDY FUNDING

This study is supported by institutional grants from Agence Nationale de la Recherche (ANR-14-CE15-0001-MECANO), Fondation pour la Recherche Médicale (Neurodon2014), and CSL Behring France.

## DISCLOSURE

B. Joubert, F. Gobert, L. Thomas, M. Saint-Martin, V. Desestret, P. Convers, V. Rogemond, G. Picard, F. Ducray, and D. Psimaras report no disclosures. J.-C. Antoine served on the scientific advisory board for Pfizer; received travel funding and/or speaker honoraria from Pfizer and Laboratoire Français des Biotechnologies et du Fractionnement; served as an associate editor for *Revue Neurologique*; and holds a patent for diagnostic test for anti-CV2/CRMP5 antibody detection. J.-Y. Delattre served on the editorial board for *The Oncologist*; received research support from Institut National du Cancer; reference center for anaplastic oligodendrogliomas. J. Honnorat reports no disclosures. Go to [Neurology.org/nn](http://Neurology.org/nn) for full disclosure forms.

Received March 3, 2017. Accepted in final form April 24, 2017.

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