

Distinct movement disorders in contactin-associated-protein-like-2 antibody associated autoimmune encephalitis: An international, retrospective, comparative cohort study

Felix Gövert*, Jos Becktepe, Bettina Balint, Christos Ganos, Ulrich Hofstadt-van Oy, Christos Krogias, James Varley, Sarosh R. Irani, Maarten J. Titulaer, Juna M. de Vries, Agnita J.W. Boon, Marco W. J. Schreurs, Bastien Joubert, Jerome Honnorat, Alberto Vogrig, Helena Ariño, Josep Dalmau, Sangeeta Scotton, Saiju Jacob, Nico Melzer, Christian Bien, Christian Geis, Jan Lewerenz, Harald Prüß, Klaus-Peter Wandinger, Günther Deuschl, Frank Leypoldt on behalf of the GENERATE Investigators

Author information:

*Corresponding author: Felix Gövert, MD, Department of Neurology, Christian-Albrecht University of Kiel and University Medical Center Schleswig-Holstein, Arnold-Heller-Str. 3, 24105 Kiel, Germany, email: govortfelix@gmail.com, Phone +49 431 500 – 23980, Fax +49 431 500 - 23988

Jos Becktepe, MD, Department of Neurology, Christian-Albrecht University of Kiel and University Medical Center Schleswig-Holstein, Arnold-Heller-Str. 3, 24105 Kiel, Germany, email: Jos.Becktepe@uksh.de

Bettina Balint, MD, Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, Queen Square London WC1N 3BG, United Kingdom and Department of Neurology, University Hospital Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany, email: b.balint@ucl.ac.uk

Christos Ganos, MD, Department of Neurology, Charité University Medicine Berlin, Charitéplatz 1, 10117 Berlin, Germany, email: cganos@gmail.com

Ulrich Hofstadt-van Oy, MD, Department of Neurology, Klinikum Westfalen, Am Knappschafts Krankenhaus 1, 44309 Dortmund, Germany, email: Ulrich.Hofstadt@klinikum-westfalen.de

Christos Krogias, MD, Department of Neurology, St Josef Hospital, Ruhr University Bochum, Gudrunstr. 56, 44791 Bochum, Germany, email: christos.krogias@ruhr-uni-bochum.de

James Varley, MD, Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, UK, email: james.varley@ndcn.ox.ac.uk

- 33 Sarosh Irani, MD, Oxford Autoimmune Neurology Group, Nuffield Department of Clinical
34 Neurosciences, University of Oxford, John Radcliffe Hospital, Headley Way, Headington,
35 Oxford OX3 9DU, UK, email: sarosh.irani@ndcn.ox.ac.uk
- 36 Maarten J. Titulaer, MD, Department of Neurology, Erasmus MC University Medical Center,
37 Dr. Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands, email:
38 m.titulaer@erasmusmc.nl
- 39 Juna M. de Vries, MD, Department of Neurology, Erasmus University Medical Center, Dr.
40 Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands, email: j.m.devries@erasmusmc.nl
- 41 Agnita J.W. Boon, MD, PhD, Department of Neurology, Erasmus MC University Medical
42 Center, Rotterdam, The Netherlands, e-mail: a.j.w.boon@erasmusmc.nl
- 43 Marco W.J. Schreurs, PhD, Department of Immunology, Erasmus MC University Medical
44 Center, Rotterdam, The Netherlands, e-mail: m.schreurs@erasmusmc.nl
- 45 Bastien Joubert, MD, PhD, Centre National de Référence pour les Syndromes Neurologiques
46 Paranéoplasiques, Hospices Civils de Lyon, Hôpital Neurologique, 59 Boulevard Pinel,
47 69677 Bron, France and Institut NeuroMyoGene INSERM U1217/CNRS UMR 5310,
48 Université de Lyon–Université Claude Bernard Lyon 1, Lyon, France, email:
49 bastien.joubert@chu-lyon.fr
- 50 Jerome Honnorat, MD, PhD, Centre National de Référence pour les Syndromes
51 Neurologiques Paranéoplasiques, Hospices Civils de Lyon, Hôpital Neurologique, 59
52 Boulevard Pinel, 69677 Bron, France and Institut NeuroMyoGene INSERM U1217/CNRS
53 UMR 5310, Université de Lyon–Université Claude Bernard Lyon 1, Lyon, France, email:
54 Jerome.honnorat@chu-lyon.fr
- 55 Alberto Vogrig, MD, PhD, Centre National de Référence pour les Syndromes Neurologiques
56 Paranéoplasiques, Hospices Civils de Lyon, Hôpital Neurologique, 59 Boulevard Pinel, 69677
57 Bron, France and Institut NeuroMyoGene INSERM U1217/CNRS UMR 5310, Université de
58 Lyon–Université Claude Bernard Lyon 1, Lyon, France, email: alberto.vogrig@gmail.com
- 59 Helena Ariño, MD, August Pi i Sunyer Biomedical Research Institute (IDIBAPS); Service of
60 Neurology, Hospital Clínic, University of Barcelona, Carrer del Rosselló, 149, 08036
61 Barcelona, Spain, email: HARINO@clinic.cat
- 62 Josep Dalmau, MD, August Pi i Sunyer Biomedical Research Institute (IDIBAPS); Service of
63 Neurology, Hospital Clínic, University of Barcelona, Carrer del Rosselló, 149, 08036
64 Barcelona, Spain and Department of Neurology, University of Pennsylvania, Philadelphia, PA
65 (USA) and Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain
66 email: Josep.Dalmau@pennmedicine.upenn.edu

Sangeeta Scotton, MD, Department of Neurology, University Hospitals Birmingham, B15 2TH United Kingdom, email: sangeeta1@doctors.org.uk

Saiju Jacob, MD, Department of Neurology, University Hospitals Birmingham, Institute of Immunology and Immunotherapy, University of Birmingham, B15 2TH United Kingdom, email: saiju.jacob@uhb.nhs.uk

Nico Melzer, MD, Department of Neurology with Institute of Translational Neurology, University of Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany, email: nico.melzer@ukmuenster.de

Christian G. Bien, MD, Epilepsy Center Bethel, Krankenhaus Mara, Maraweg 21, 33617 Bielefeld, Germany, email: Christian.bien@gmx.de

Christian Geis, MD, Department of Neurology, University of Jena, Am Klinikum 1, 07747 Jena, Germany, email: christian.geis@med.uni-jena.de

Jan Lewerenz, MD, Department of Neurology, University of Ulm, Oberer Eselsberg 45, 89081 Ulm, Germany, email: jan.lewerenz@uni-ulm.de

Harald Prüß, MD, Department of Neurology, Charité University Medicine Berlin, Charitéplatz 1, 10117 Berlin, Germany, email: harald.pruess@dzne.de

Klaus-Peter Wandinger, MD, Neuroimmunology, Institute of Clinical Chemistry and Department of Neurology, University of Luebeck and University Medical Center Schleswig-Holstein, Ratzeburger Allee 160, 23538 Lübeck, Germany, email: klaus-peter.wandinger@uksh.de

Günther Deuschl, MD, Department of Neurology, Christian-Albrecht University of Kiel and University Medical Center Schleswig-Holstein, Arnold-Heller-Str. 3, 24105 Kiel, Germany, email: g.deuschl@neurologie.uni-kiel.de

Frank Leypoldt, MD, Neuroimmunology, Institute of Clinical Chemistry and Department of Neurology, Christian-Albrecht University of Kiel and University Medical Center Schleswig-Holstein Arnold-Heller-Str. 3, 24105 Kiel, Germany, email: Frank.Leypoldt@uksh.de

Running head: Movement disorders in the context of CASPR2 antibodies

Key words: CASPR2, LGI1, myoclonus, autoimmune encephalitis, movement disorders, neuronal autoantibodies

Abstract (274 words)

Background Contactin-associated-protein-like-2 (CASPR2) autoimmunity can manifest with immunotherapy-responsive movement disorders sometimes mimicking non-inflammatory etiologies. We aimed to systematically assess their prevalence and manifestation in patients with CASPR2-autoimmunity.

Methods This international, retrospective cohort study included patients with CASPR2-autoimmunity from participating expert centers in Europe. Patients with ataxia and/or movement disorders were analyzed in detail using questionnaires and video recordings. We recruited a comparator group with anti-leucin-rich-glioma-inactivated-1 (LGI1) encephalitis from the GENERATE network. Characteristics were compared according to serostatus.

Findings We identified 164 patients with CASPR2 autoantibodies (aabs). Of these, 149 (90.8%) had only CASPR2- and 15 (9.1%) both CASPR2- and LGI1-aabs. Compared to 105 patients with LGI1 encephalitis, patients with CASPR2-aabs more often had movement disorders and ataxia (35.6% versus 3.8%; $p < 0.001$). This was evident in all subgroups: ataxia 22.6% versus 0.0%, myoclonus 14.6% versus 0.0%, tremor 11.0% versus 1.9%, or combinations thereof 9.8% versus 0.0% (all $p < 0.001$). The small group of patients double positive for LGI1/CASPR2-aabs (15/164) significantly more frequently had myoclonus, tremor, “mixed movement disorders”, Morvan syndrome and underlying tumours.

We observed distinct movement disorders in CASPR2-autoimmunity (14.6%): episodic ataxia (6.7%), paroxysmal orthostatic segmental myoclonus of the legs (3.7%) and continuous segmental spinal myoclonus (4.3%). These occurred together with further associated symptoms or signs suggestive of CASPR2 autoimmunity. However, two/164 patients (1.2%) had isolated segmental spinal myoclonus.

Interpretation Movement disorders and ataxia are highly prevalent in CASPR2-autoimmunity. Paroxysmal orthostatic segmental myoclonus of the legs is a novel albeit rare manifestation. Further distinct movement disorders include isolated and combined segmental spinal myoclonus and autoimmune episodic ataxia.

Funding German Ministry of Education and Research (01GM1908A, Leypoldt). French National Research Agency (ANR), “*Investissements d’Avenir*” (ANR-18-RHUS-0012-BETPSY, Honnorat).

Research in context*Evidence before this study*

Autoimmune encephalitis (AE) can be classified into antibody-defined subtypes, many of which can manifest with prominent movement disorders. In the elderly, anti-leucine-rich glioma-inactivated-1 (LGI1) and contactin-associated-protein-like-2 (CASPR2) antibody-associated diseases compose a relevant fraction of AE and are often immunotherapy responsive. Patients with LGI1 autoantibodies (aabs) are known to present with limbic encephalitis and additionally faciobrachial dystonic seizures (FBDS), but the clinical spectrum of CASPR2 aabs-associated disorders is more diverse: limbic encephalitis, Morvan's syndrome, peripheral nerve hyperexcitability syndrome, ataxia, pain and sleep disorders occur. Furthermore, reports on unusual, sometimes isolated and immunotherapy-responsive movement disorders in CASPR2-aabs-associated syndromes have caused substantial concern regarding necessity of aabs-testing in patients with movement disorders. We searched MEDLINE for articles published before May 2021 using MeSH terms: "autoimmune encephalitis", "movement disorders", "chorea", "myoclonus", "ataxia", "faciobrachial dystonic seizures", "parkinsonism", "tremor", "CASPR2", "LGI1". We restricted searches to human studies and also reviewed references indicated by papers identified in this search.

Added value of this study

This European, retrospective cohort study systematically provides clinical data on the largest series of patients with CASPR2-autoimmunity to date collected by reference centers specialized on AE from five countries together representing more than 280 million Europeans. As a comparator group, a large cohort of patients with LGI1-aabs from the German GENERATE network was included. Our study demonstrates that movement disorders are common in CASPR2-autoimmunity including a diverse spectrum of manifestations while movement disorders other than FBDS are rare in LGI1-AE. Importantly, it describes two paroxysmal movement disorders which can appear concomitant, after or even before the development of classic symptoms of CASPR2-autoimmunity: Paroxysmal orthostatic segmental myoclonus of the lower limbs and autoimmune episodic ataxia. Further we demonstrate that in rare instances CASPR2-autoimmunity can cause continuous, isolated spinal segmental myoclonus. Importantly, these movement disorders of patients in our study responded to immunotherapy. Our study provides instructive video material of these unusual movement disorders for neurologists.

Implications of all available evidence

Our study (1) increases awareness in neurologists and allows movement disorder specialists and neuroimmunologists worldwide to sharpen their clinical picture of CASPR2-autoimmunity, (2) helps practitioners to better diagnose and treat CASPR2-autoimmunity by providing clinico-serological correlations and data on tumor frequency and (3) suggests to consider testing for neuronal aabs and specifically for CASPR2-aabs in particular in elderly male patients with paroxysmal movement disorders or spinal segmental myoclonus even without other overt clinical and paraclinical signs of AE.

Introduction

Autoimmune encephalitis (AE) are increasingly recognized, albeit rare, disorders of the nervous system. They affect all age groups, are often treatment responsive and in many cases antibodies targeting neuronal surface antigens can be detected. In the elderly, autoimmune syndromes with autoantibodies (aabs) targeting leucine-rich-glioma-inactivated-1 (LGI1) or contactin-associated-protein-like-2 (CASPR2) compose a relevant fraction of seropositive AE. Their early recognition is paramount because response to immunotherapy and outcome are frequently favorable¹⁻³. The classical syndrome of LGI1-encephalitis consists of limbic encephalitis (LE) with preceding or concurrent faciobrachial dystonic seizures (FBDS)⁴. The clinical spectrum associated with CASPR2-aabs is considerably more diverse. The disease preferentially affects elderly men with subacute to chronic progressive combinations of cognitive decline, epilepsy, autonomic dysfunction, ataxia, insomnia, neuromyotonia, neuropathic pain and weight loss³.

We have previously identified a patient with severely incapacitating myoclonus of the lower limbs while standing without overt signs of AE who was misdiagnosed as suffering from a functional movement disorder⁵. After detection of CASPR2-aabs, he responded very favorable to immunotherapy. Recently, autoimmune episodic ataxia has also been described as a manifestation of CASPR2-autoimmunity^{6, 7}. These observations and further cases we were informed of since have provided the rationale for the current study. Therefore, we aimed to investigate the general characteristics, frequencies and specific patterns of movement disorders and ataxia in a large European cohort of patients with CASPR2-aabs. In particular, we wanted to determine whether we could identify further patients with the peculiar syndrome we tentatively labelled *paroxysmal orthostatic segmental myoclonus of the lower limbs* as a previously unrecognized manifestation of CASPR2-autoimmunity.

Methods

Study design and participants

This international, retrospective cohort study was done by analysis of patients records, follow-up and - if available - video sequences of all patients with AE and detection of CASPR2-aabs being followed in specialized centers/study groups in Europe. We included patients with CASPR2-autoimmunity diagnosed between January 1994 and August 2019 in one of the participating centers (alphabetic by city name: Hospital Clinic, Barcelona, Spain; Epilepsy-

Center-Bethel, Bielefeld, Germany; Clinical Chemistry, University-Hospital-Schleswig-Holstein Kiel/Lübeck, Germany; Centre-de-Référence-National-Syndromes-Neurologiques-Paranéoplasiques, Lyon, France; Oxford-Autoimmune-Neurology-Group, Oxford, UK; Center-of-Experimental-Neuroimmunology, Erasmus-MC-Medical-Center, Rotterdam, The Netherlands) and all CASPR2-aabs positive patients recruited by the German-Network-for-Research-on-Autoimmune-Encephalitis (GENERATE;en.generate-net.de). As a comparator, we recruited patients with LGI1-AE in the GENERATE registry (January 2014-August 2019). Participating laboratories utilized different testing systems and strategies. However, all participating laboratories adhered to rigorous and published criteria to ensure specificity and exclude patients with isolated unspecific low titer serum CASPR2-aabs (summarized in supplementary methods). Participating authors from each center retrospectively reviewed records from patients, focusing on available information on movement disorders, completed standardized questionnaires in case movement disorders were present and responded to queries. All expert centers were asked to provide a syndrome diagnosis (LE, Morvan's syndrome, AE etc.^{8, 9}) and rate presence or absence of grouped clinical symptoms (e.g. psychiatric symptoms, movement disorders, etc.). MRI was classified as suspicious for AE if uni- or bilateral T2/FLAIR temporal lobe changes were present⁸. Physicians were specifically asked for prominent myoclonus as the leading complaint confirmed clinically electrophysiologically. Written informed consent was obtained from all patients with approval of the local ethical committees of participating centers. Signed patient consent was obtained for videos. Nine/164 patients with CASPR2-autoimmunity were previously reported^{5, 6, 10, 11}.

Statistical analysis

Primary outcome of this analysis was the overall prevalence of any movement disorder and/or ataxia in patients with CASPR2-aabs compared to patients with LGI1-encephalitis. Secondary outcomes were differences in movement disorder subtypes and clinical/demographic characteristics between this group and also CASPR2-/LGI1-aabs double positive patients. We analyzed differences between group medians of clinical characteristics using Kruskal-Wallis with post-hoc testing or Mann-Whitney U test as applicable for non-normally distributed data and the Fisher-Freeman-Halton-Extension of the Fisher's Exact test (for $r \times c$ contingency tables) with post-hoc testing for group differences regarding categorical variables. Because this was an exploratory approach, we did not correct for multiple testing in secondary endpoints, therefore we interpreted p-values between 0.005 and 0.05 with caution. We used SPSS (ver22)/GraphPad-Prism 8 for analyses.

Role of the funding source

The study sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Clinical and demographic data

We enrolled 164 patients with CASPR2-aabs associated autoimmune syndromes. Of these, 149 had isolated CASPR2-aabs (CASPR2-cohort) and 15 patients were tested double-positive for CASPR2- and LGI1-aabs (CASPR2/LGI1-cohort). Additionally, we included 105 patients with LGI1-AE with isolated LGI1-aabs (LGI1-cohort) as a comparator cohort (Figure 1). Of note, patients double-positive for CASPR2- and LGI1-aabs had significantly different syndrome diagnoses, clinical symptoms and diagnostic characteristics compared to the LGI1- but also the CASPR2-cohort. Clinical and demographic data are summarized in table 1 and 2.

Ataxia and movement disorders

Of all patients, 25.3% (68/269) had associated movement disorders and/or ataxia. The prevalence was highest in patients with double-positivity for CASPR2- and LGI1-aabs (73%, 11/15) compared to patients with CASPR2-aabs (35.6%, 53/149; $p=0.005$) or LGI1-aabs (4%, 4/105; $p<0.001$) alone (Table 1, supplemental table 1). The spectrum and overlap of ataxia and movement disorders in patients with CASPR2-aabs was diverse: patients with CASPR2-aabs often had ataxia (20.8%, 31/149), myoclonus (10.1%, 15/149) and/or tremor (8.1%, 12/149). Chorea (7.5%, 4/149) and parkinsonism (3.8%, 2/149) were only rarely present. Patients double positive for CASPR2- and LGI1-aabs even more often presented with myoclonus (60%, 9/15), ataxia (40%, 6/15) and tremor (40%, 6/15). In contrast, patients with LGI1-aabs had FBDS in 25% (26/105) but other than that only rarely presented with movement disorders including subacute generalized chorea (2%, 2/105) and prominent postural tremor of the upper limbs (2%, 2/105).

Combinations and temporal patterns of ataxia and movement disorders

Most patients independent of underlying aabs had single movement disorders or ataxia (77%, 52/68). Mixed movement disorders only occurred in patients with CASPR2-aabs (6.0%) or with CASPR2/LGI1-aabs (47%, Table 1, Figure 2). In general, mixed movement disorders

predominantly occurred as a combination of ataxia either with myoclonus, tremor or the combination of all three (Figure 2). In most cases, ataxia and movement disorders occurred in combination with other CASPR2-spectrum symptoms (combined movement disorders), e.g. cognitive dysfunction. In patients with CASPR2-autoimmunity, most patients with movement disorders had either LE (55%, 29/53) or Morvan's syndrome (CASPR2-aab positive 17% [9/53], CASPR2/LGI1-double positive 91%, [10/11]). However, in some patients with CASPR2-aabs, the movement disorder or ataxia was the presenting symptom and remained the dominant clinical symptom during the course of the disease: Eight patients (4.9%) presented with a pure isolated movement disorder or ataxia. Of these, six patients (3.7%) suffered from an isolated cerebellar syndrome and two patients had an isolated segmental spinal myoclonus (1.2%).

CASPR2-associated Ataxia

Next, we analyzed patients with prominent ataxia (Supplemental table 3) within the CASPR2-autoimmunity cohort (independent of LGI1-aabs status). 22.6% (37/164) in the combined CASPR2-autoimmunity cohort had prominent ataxia in the course of the disease. Apart of the above mentioned six patients with an isolated subacute cerebellar syndrome, most patients with ataxia (31/37; 84%) had additional classic CASPR2-associated symptoms. Nevertheless, ataxia was the presenting or one of the presenting symptoms in 73% (22/30). The vast majority of patients presented with prominent gait ataxia (32/34; 94%) while limb ataxia was seen in 68% (19/28) and cerebellar dysarthria was noted in 59% (16/27). Immunotherapy improved ataxia in 67% (16/24) of patients. Interestingly, 11 patients presented with paroxysmal attacks of ataxia mimicking classic episodic ataxia (see patient video 1). All patients had prominent gait ataxia while cerebellar dysarthria and limb dysmetria was noted in 7 patients each. Such episodes were mostly triggered by orthostatism (9/11) and generally had a short duration up to a few minutes. Almost all patients (10/11) with paroxysmal cerebellar ataxia had limbic encephalitis and occurred either before (n=3), concomitant (n=2) or after (n=5) development of limbic symptoms. Immunosuppressive treatment resulted in complete cessation of such paroxysmal attacks. Compared to patients without ataxia, ataxic patients in the CASPR2-cohort more often had thymomas (24% vs. 9%; $p=0.03$) and worse functional status at last-follow-up ($p=0.002$; supplemental table 3). Further details are summarized in the supplemental table 3.

CASPR2-associated myoclonus

A total of 24 patients (14.6%; 24/164) with CASPR2-autoimmunity had prominent myoclonus during the course of the disease (Table 3, supplemental table 4). Myoclonus mostly occurred in combination with associated CASPR2 clinical features (92%) but infrequently also isolated (8%, 2/24; Figure 3). Myoclonus was the presenting symptom or one of the presenting symptoms in 46% (11/24), otherwise onset ranged between 1 month to 48 months from first symptom onset. Combined myoclonus presented either as generalized (36%, 8/22) or segmental myoclonus (50%, 11/22; 3/22 distribution unknown).

Segmental myoclonus was restricted to the lower limbs in six (54%, 6/11) and the upper limbs in three patients (27%, 3/11). Two patients presented with segmental myoclonus of both the abdomen and lower limbs (18%, 2/11) (Supplemental video 2: patient 2). Interestingly, all six patients with segmental myoclonus restricted to the lower limbs presented with short lasting paroxysmal attacks of myoclonus triggered by orthostatism (n=3) or both walking and orthostatism (n=3) (Figure 4, supplemental video 3: patients 1-4). Therefore we tentatively labelled these attacks as *paroxysmal orthostatic segmental myoclonus of the lower limbs*. They predominantly had a duration of 10-30 seconds and occurred multiple times with a maximum of 50 times a day. In four patients they were one of the presenting symptoms while in two patients myoclonus occurred few months after disease onset (neuropathic pain and epileptic seizures). In all patients, myoclonus occurred together with or prior to development of further CASPR2 core symptoms. One patient had classic limbic encephalitis while the remaining patients had Morvan's syndrome (n=3), brain stem dysfunction or a combination of epileptic seizures and dysarthria (n=1 each). All were highly impaired due to severe imbalance and falls during the attacks. Immunosuppressive treatment resulted in complete alleviation (n=5) or major improvement (n=1) of myoclonus of the lower limbs. Of note, in the majority of patients with generalized myoclonus (62%, 5/8) myoclonus of the legs markedly aggravated during orthostatism and/or walking resulting in considerable balance problems.

Two patients presented with an isolated prominent spinal segmental myoclonus restricted to the abdominal muscles without any further clinical symptoms in particular no evidence for any CASPR2 core symptoms (Figure 3, Supplemental video 2: patient 1). In both patients surface-EMG demonstrated simultaneous and stereotypical myoclonic bursts with a frequency of 1-2hz and a duration between 350-450ms in several muscles with contiguous spinal cord innervation between Th10 and L3 (Supplemental figure 1).

In general, patients with myoclonus (compared to patients without) had a higher prevalence of coexisting tumour (42%; usually thymoma 38%), Morvan's syndrome (46%),

CASPR2/LGI1-double seropositivity (38%), higher maximum mRS scores ($p=0.001$), sleep abnormalities (63%), autonomic symptoms (58%) and tremor (33%). LE (21%), epileptic seizures (38%) and dyscognitive symptoms (50%) were less prevalent. MRI imaging did not show specific findings in 91% (19/21) of patients with myoclonus. Of note, neither CSF nor MRI imaging was suspicious of inflammatory causes in the majority of patients with prominent myoclonus in the context of CASPR2 autoimmunity (75%, 15/20 vs. 34%, 30/89; $p=0.001$). Indeed, four patients with prominent myoclonus were initially diagnosed as suffering from a functional movement disorder based on inconspicuous general diagnostic testing and appropriate treatment was delayed up to two years. Immunotherapy mostly consisting of heterogeneous combined regimens of steroids, ivIG, plasma exchange, rituximab lead to complete alleviation or major improvement of myoclonus in 79% (19/24).

CASPR2-associated tremor

11% (18/164) of patients in with CASPR2-autoimmunity presented with prominent tremor. All patients had additional classic CASPR2-associated symptoms but tremor was present at disease onset in 60% (9/15) of cases mostly presenting with a generalized action tremor (67%, 10/15) and with a favourable response to immunotherapy in 73% (11/15). Similar to CASPR2-associated myoclonus, patients with prominent tremor significantly more frequent suffered from Morvan's syndrome (50%), coexisting malignoma (50%, mostly thymoma (44%)) autonomic dysfunction (67%), sleep abnormalities (77%), ataxia (44%) and myoclonus (44%) (see supplemental table 5).

Discussion

In this large, retrospective cohort study, we show that (1) movement disorders, primarily ataxia, myoclonus and tremor, are a common and prominent feature in patients with CASPR2-aabs, (2) a characteristic, immunotherapy-responsive novel paroxysmal movement disorder exists that we labelled *paroxysmal orthostatic segmental myoclonus of the lower limbs* and which can occur associated to CASPR2-aabs, (3) further therapy-responsive distinct syndromes associated with CASPR2-autoimmunity are autoimmune episodic ataxia and continuous segmental spinal myoclonus and (4) that these movement disorder/atactic syndromes usually occur together with further CASPR2-autoimmunity associated symptoms yet sometimes compose the initial and rarely isolated symptom.

In general, we observed prominent movement disorders in a quarter of our combined cohorts, which was lowest in the LGI1- (4%), moderate in the CASPR2-cohort (36%) and highest in

patients with combined CASPR2- and LGI1-aabs (73%). The pattern of movement disorders considerably differed between patients with CASPR2-aabs, LGI1-aabs and a combination of both. FBDS were seen in 25% of our patients with LGI1-AE and their presence strongly points towards underlying LGI1-aabs associated syndromes, while ataxia and prominent myoclonus are a feature of CASPR2-aabs autoimmunity.

In this study we observed three characteristic and distinct clinical patterns of movement disorders in patients with CASPR2-associated syndromes which may occur before, concomitant or after the development of classic CASPR2-associated symptoms. Although CASPR2-core symptoms were mostly detectable in those patients, the corresponding movement disorder was frequently the dominant clinical symptom and initial misdiagnosis was common resulting in significant treatment delay. Within each group, patients shared a remarkable similarity in manifestation, trigger factors and diagnostic findings:

(1) In the first group, patients presented with a paroxysmal movement disorder characterized by sudden, brief and repetitive attacks of myoclonus precipitated by orthostatism. In contrast to the predominantly genetically determined paroxysmal dyskinesias which usually have onset in child- or early adulthood and mostly present with self-limiting, short lasting episodes of dystonia and/or chorea¹², our patients were elderly male patients who presented with short-lasting attacks of severe myoclonus of the lower limbs resulting in considerable shaking on standing. Several conditions including orthostatic myoclonus, drug-induced (i.a. tricyclic antidepressants and antipsychotic drugs) action myoclonus of the legs, postanoxic myoclonus and epileptic conditions such as familial cortical myoclonic tremor with epilepsy should be considered in patients suffering from prominent myoclonus while standing¹³. Furthermore generalized polymyoclonus caused by different paraneoplastic and autoimmune conditions may result in significant stance and gait impairment¹⁴. Though the paroxysmal character triggered by orthostatism clearly differentiates our reported patients and seems to be a distinct feature of CASPR2 autoimmunity.

(2) Indeed, a second group of patients in our study also presented short-lasting paroxysmal episodes but with cerebellar gait ataxia. Intriguingly those episodes were also triggered by orthostatism and likewise immunotherapy resulted in good improvement. While such transient cerebellar symptoms were nearly without exception associated with limbic encephalitis, paroxysmal orthostatic segmental myoclonus was mostly associated with Morvan syndrome and brainstem encephalitis possibly indicating

different underlying pathophysiology of both paroxysmal disorders. Prior studies have already described stereotyped paroxysmal episodes considered cerebellar ataxia in a smaller number of patients with CASPR2-aab associated AE^{6, 7, 10, 15}. Similar as in our study orthostatism and walking provoked recurrent attacks and immunotherapy resulted in good clinical improvement^{6, 10}. Interestingly, due to the striking clinical overlap with hereditary channelopathies like episodic ataxia type 1, ion channel dysfunction was considered to play a potential pathophysiological role in CASPR2-aab associated paroxysmal symptoms⁶. Indeed, most neurological paroxysmal disorders are linked by a common pathophysiological feature namely neuronal hyperexcitability which is a well-known hallmark of CASPR2-associated syndromes like neuromyotonia, Morvan's syndrome and LE.

(3) Finally, a third group of patients presented with a continuously present segmental myoclonus and sometimes even isolated myoclonus without any further neurological abnormalities and favorable response to immunotherapy. In both patients with an isolated segmental myoclonus appropriate electrophysiology was performed and diagnosis of a spinal segmental myoclonus was proven. A similar case with an isolated spinal myoclonus restricted to both lower limbs associated with CASPR2-aabs was recently reported in the context of thymoma-associated myasthenia gravis which completely ceased after chemotherapy¹⁶. Our observations and this case demonstrate that CASPR2-aabs associate with spinal segmental myoclonus and that myoclonus can even be the only clinical symptom. Spinal segmental myoclonus is caused by a loss of inhibition of spinal interneurons leading to hyperexcitation of anterior horn cells¹⁷. Interestingly, CASPR2 is an important transmembrane protein which clusters KV1.1 and KV1.2 VGKCs at the juxtaparanodes of myelinated axons in the CNS and PNS and helps to maintain the internodal resting potential and avoids repetitive firing¹⁸⁻²⁰. Furthermore, CASPR2 is widely expressed by inhibitory neurons in the CNS²¹. Accordingly, antibodies targeting CASPR2 might result in disruption of CASPR2 interactions within the transmembrane complex of VGKC which might cause nerve hyperexcitability and myoclonus, respectively.

All three types of movement disorders carry a high level of recognition, once their clinical pictures are appreciated by neurologists and their clinical picture can be observed in the supplemental videos 1-3. In particular in patients with myoclonus the bizarre clinical presentations often resulted in misdiagnosis of functional movement disorders in several of

our patients and our index case^{5, 10}. Indeed, myoclonus and particular axial myoclonus is a common clinical feature in patients suffering from a functional movement disorder and electrophysiology is essential to verify the diagnosis²²⁻²⁴. Unfortunately, appropriate electrophysiology was not performed in most patients with paroxysmal myoclonus, but in both patients with an isolated segmental myoclonus spinal origin was proven via electrophysiology. Importantly, none of the patients had additional symptoms suggestive of a functional movement disorder and immunotherapy resulted in major improvement. Of note, neither brain MRI imaging nor CSF analysis were helpful in identifying the underlying autoimmune condition in most myoclonus patients; three quarter of patients had neither medial temporal lobe T2/FLAIR hyperintensities nor inflammatory CSF changes.

Our study might also supports previous reports^{25,26-28} that within the group of patients with CASPR2-autoimmunity, different subgroups might exist. In our case series, a double positivity for CASPR2- and LGI1-aabs associated with the presence of myoclonus, tremor, ataxia and Morvans syndromes often together with thymomas and absence of inflammatory CSF and MRI changes. Furthermore, we observed a high frequency of patients without MRI- and CSF changes suggestive of underlying autoimmunity: 92 of the CASPR2/LGI1-cohort, 35% of the CASPR2-cohort and 20% of the LGI1 cohort did neither have medial temporal lobe abnormalities nor CSF pleocytosis or isolated oligoclonal bands²⁹. One explanation is that testing and diagnosis in LGI1- and CASPR2-ab associated diseases is often performed several months after onset of symptoms due to insidious onset and frequency of inflammatory CSF changes are known to decline with time from onset³⁰. Nevertheless, clinical decision making should not exclude underlying CASPR2 nor LGI1-autoimmunity in cases without suggestive CSF and MRI findings.

The main limitations of our study result from the retrospective design, the recruitment strategy focused on expert centers for autoimmune encephalitis and detection of symptoms using questionnaires. Therefore, the estimate of prevalence and incidence of symptoms in patients and in particular isolated movement disorders due to CASPR2-autoimmunity is prone to ascertainment and detection bias. Furthermore, the LGI1-cohort used as a comparator was retrospectively recruited from the national GENERATE database and might have a different selection/reporting bias compared to the CASPR2-cohort. Especially the lack of myoclonus in the LGI1 cohort is contrary to some previous studies which described myoclonus in 29-80% of LGI1 positive patients^{31, 32}. We believe this to be due to misconception of FBDS for myoclonus in some instances in those reports but we can not rule out underreporting in our LGI1-cohort. Especially the CASPR2/LGI1 cohort was very small (n=15), which makes this

group especially prone to selection bias. Nevertheless, coexistence of LGI1 and CASPR2 aabs in patients should trigger diagnostics for underlying paraneoplastic origin especially due to thymoma²⁵⁻²⁷. Future prospective trials of sufficiently large cohorts of patients with CASPR2 but also LGI1-autoimmunity in specialized movement disorder centers would be desirable to address these limitations. Another limitation is the heterogeneity of antibody testing strategies used by the participating laboratories. However, we utilized either confirmatory testing approaches or high cut-off values for serum testing to prevent including false-positive patients with other underlying diseases. This last aspect is very important in clinical practice: The widely used commercial cell-based assays for CASPR2 should be interpreted with caution at low serum dilutions and confirmation sought in positive cases¹.

In conclusion, we demonstrate that movement disorders primarily ataxia, myoclonus and tremor are common in patients with CASPR2 and CASPR2-/LGI1 aabs, the pattern and prevalence of movement disorders differs between patients with LGI1-, CASPR2- (and possibly LGI1/CASPR2)-aabs and that a subgroup of CASPR2 patients may present with therapy-responsive paroxysmal episodes of either ataxia or myoclonus or even isolated continuous spinal segmental myoclonus. Therefore CASPR2 autoimmunity should be considered as a differential diagnosis especially in elderly male patients who present with isolated or combined spinal segmental myoclonus, paroxysmal myoclonus of the lower limbs and paroxysmal ataxia triggered by orthostatism or walking. This is of particular clinical importance because movement disorders and associated symptoms showed favorable response to immunotherapy in our cohort.

Data sharing statements

Any data not published within this article are available after publication, at the Kiel University (by contacting the corresponding author). Patient-related data will be shared upon request from any qualified investigator, maintaining anonymization of the individual patients.

Declaration of interests

FG reports no disclosures.

JB reports no disclosures.

BB reports no disclosures.

CG was supported by a Freigeist Fellowship from the VolkswagenStiftung. He also received honoraria serving as ad hoc advisory board for Biomarin Pharmaceutical and for educational activities from the Movement Disorder Society.

512 UHvO received Speaker honoraria from Merck and Bayer Healthcare, honoraria for
513 participating in an advisory board from Roche as well as research support by unrestricted
514 grants from Bayer-Schering, Novartis, Merck.

515 CK discloses honoraria and travel grants for scientific meetings from Bayer Vital and Daiichi
516 Sankyo.

517 JV reports no disclosures

518 SRI reports no disclosures

519 MT reports grants from Dutch Epilepsy Foundation (14-19 and 19-18), grants from
520 Netherlands Organisation for Scientific Research (memorable incentive), NWO / ZonMW,
521 grants from Dioraphte, grants from Erasmus MC fellowship, grants from Euroimmun AG,
522 grants from MedImmune LLC, grants from Guidepoint Global LLC, grants from Novartis,
523 outside the submitted work; In addition, Dr. Titulaer has a patent "methods for typing
524 neurological disorders and cancer, and devices for use therein" pending to Erasmus MC.

525 JdV reports no disclosures.

526 BJ reports no disclosures.

527 JH discloses speaker honoraria from CSL Behring, travel funding from Abbvie. He works for
528 an academic institution, which offers antibody testing on a commercial basis to academic and
529 non-academic institutions.

530 AV reported receiving a fellowship grant from the European Academy of Neurology (EAN)

531 HA reports no disclosures.

532 JD reports no disclosures.

533 SS reports no disclosures.

534 SJ has served as an international advisory board member for Alexion and Alnylam
535 pharmaceuticals, is currently an expert panel member of Myasthenia Gravis consortium for
536 Argenx pharmaceuticals, and has received speaker fees from Terumo BCT and Eisai
537 pharmaceuticals. None of these are relevant to the current study.

538 NM has received honoraria for lecturing and travel expenses for attending meetings from
539 Biogen Idec, GlaxoSmith Kline, Teva, Novartis Pharma, Bayer Healthcare, Genzyme,
540 Alexion Pharmaceuticals, Fresenius Medical Care, Diamed, and BIAL, and has received
541 financial research support from Euroimmun, Fresenius Medical Care, Diamed, Alexion
542 Pharmaceuticals, and Novartis Pharma.

543 CGB obtained honoraria for speaking engagements from UCB (Monheim, Germany) and
544 Desitin (Hamburg, Germany). He receives research support from the Deutsche

Forschungsgemeinschaft (German Research Council, Bonn, Germany) and Gerd-Altenhof-Stiftung (Deutsches Stiftungs-Zentrum, Essen, Germany).

CG discloses speaker honoraria from Alexion, travel funding from Merck, and serving on advisory boards for Roche.

JL reports no disclosures

KPW reports no disclosures

GD reports personal fees from Boston Scientific, Jazz, Functional Neuromodulation, Thieme publishers, grants from Medtronic, outside the submitted work. He receives funding for his research from the German Research Council (SFB 1261, T1).

FL discloses speaker honoraria from Biogen, Bayer, Roche, Novartis and serving on advisory boards for Roche, Biogen and Alexion. He works for an academic institution, which offers antibody testing.

Acknowledgments

We would like to thank all patients participating in this study and all active and past members and contributors of the German Network for Research on autoimmune encephalitis.

Documentation of 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 of the first draft, B. Review and Critique

FG: 1A, 1B, 1C, 2A, 2B, 3A, 3B

JS: 1C, 3B

BB: 1C, 3B

CG: 1C, 3B

UHvO: 1C, 3B

CK: 1C, 3B

JV: 1C, 3B

SRI: 1C, 3B

MT: 1C, 3B

JdV: 1C, 3B

BJ: 1C, 3B

JH: 1C, 3B

579 AV: 1C, 3B
580 HA: 1C, 3B
581 JD: 1C, 3B
582 SS: 1C, 3B
583 SJ: 1C, 3B
584 NM: 1C, 3B
585 CB: 1C, 3B
586 CG: 1C, 3B
587 JL: 1C, 3B
588 HP: 1C, 3B
589 KPW: 1C, 3B
590 GD: 1C, 3B
591 FL: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B
592

593 References

- 594 1. Bien CG, Mirzadjanova Z, Baumgartner C, et al. Anti-contactin-associated protein-2
595 encephalitis: relevance of antibody titres, presentation and outcome. *European journal of neurology*
596 2017;24(1):175-186.
- 597 2. Irani SR, Stagg CJ, Schott JM, et al. Faciobrachial dystonic seizures: the influence of
598 immunotherapy on seizure control and prevention of cognitive impairment in a broadening
599 phenotype. *Brain : a journal of neurology* 2013;136(Pt 10):3151-3162.
- 600 3. van Sonderen A, Arino H, Petit-Pedrol M, et al. The clinical spectrum of Caspr2 antibody-
601 associated disease. *Neurology* 2016;87(5):521-528.
- 602 4. Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lgi1 antibody
603 limbic encephalitis. *Annals of neurology* 2011;69(5):892-900.
- 604 5. Gövert F, Witt K, Erro R, et al. Orthostatic myoclonus associated with Caspr2 antibodies.
605 *Neurology* 2016;86(14):1353-1355.
- 606 6. Joubert B, Gobert F, Thomas L, et al. Autoimmune episodic ataxia in patients with anti-
607 CASPR2 antibody-associated encephalitis. *Neurology(R) neuroimmunology & neuroinflammation*
608 2017;4(4):e371.
- 609 7. Lopez Chiriboga AS, Pittock S. Episodic ataxia in CASPR2 autoimmunity. *Neurology(R)*
610 *neuroimmunology & neuroinflammation* 2019;6(2):e536.
- 611 8. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune
612 encephalitis. *Lancet neurology* 2016;15(4):391-404.
- 613 9. Irani SR, Pettingill P, Kleopa KA, et al. Morvan syndrome: clinical and serological observations
614 in 29 cases. *Annals of neurology* 2012;72(2):241-255.
- 615 10. Krogias C, Hoepner R, Muller A, Schneider-Gold C, Schroder A, Gold R. Successful treatment
616 of anti-Caspr2 syndrome by interleukin 6 receptor blockade through tocilizumab. *JAMA neurology*
617 2013;70(8):1056-1059.
- 618 11. Scotton S, See M, Cahill V, et al. CASPR2 antibody-related movement disorders: case series.
619 *Journal of neurology* 2021;268(4):1533-1535.
- 620 12. Gardiner AR, Jaffer F, Dale RC, et al. The clinical and genetic heterogeneity of paroxysmal
621 dyskinesias. *Brain : a journal of neurology* 2015;138(Pt 12):3567-3580.

13. Erro R, Bhatia KP, Cordivari C. Shaking on Standing: A Critical Review. *Mov Disord Clin Pract* 2014;1(3):173-179.
14. McKeon A, Pittock SJ, Glass GA, et al. Whole-body tremulousness: isolated generalized polymyoclonus. *Archives of neurology* 2007;64(9):1318-1322.
15. Sousa S, Guerreiro R, Carmona C, Gouveia LO, Pita F. Caspr2 antibodies in a patient with prostate cancer: a cognitive deterioration with recurrent and paroxysmal gait ataxia and aphasia. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 2017;38(12):2217-2219.
16. Hines H, Murray NM, Ahmad S, Jaradeh S, Gold CA. Video NeurolImages: Paraneoplastic spinal myoclonus associated with Caspr2 antibodies. *Neurology* 2018;90(14):660-661.
17. Di Lazzaro V, Restuccia D, Nardone R, et al. Changes in spinal cord excitability in a patient with rhythmic segmental myoclonus. *Journal of neurology, neurosurgery, and psychiatry* 1996;61(6):641-644.
18. Rasband MN, Trimmer JS, Schwarz TL, et al. Potassium channel distribution, clustering, and function in remyelinating rat axons. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 1998;18(1):36-47.
19. Devaux J, Gow A. Tight junctions potentiate the insulative properties of small CNS myelinated axons. *The Journal of cell biology* 2008;183(5):909-921.
20. Saint-Martin M, Pieters A, Dechelotte B, et al. Impact of anti-CASPR2 autoantibodies from patients with autoimmune encephalitis on CASPR2/TAG-1 interaction and Kv1 expression. *Journal of autoimmunity* 2019;103:102284.
21. Penagarikano O, Abrahams BS, Herman EI, et al. Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell* 2011;147(1):235-246.
22. van der Salm SM, Erro R, Cordivari C, et al. Propriospinal myoclonus: clinical reappraisal and review of literature. *Neurology* 2014;83(20):1862-1870.
23. Esposito M, Edwards MJ, Bhatia KP, Brown P, Cordivari C. Idiopathic spinal myoclonus: a clinical and neurophysiological assessment of a movement disorder of uncertain origin. *Movement disorders : official journal of the Movement Disorder Society* 2009;24(16):2344-2349.
24. van der Salm SM, Koelman JH, Henneke S, van Rootselaar AF, Tijssen MA. Axial jerks: a clinical spectrum ranging from propriospinal to psychogenic myoclonus. *Journal of neurology* 2010;257(8):1349-1355.
25. Joubert B, Saint-Martin M, Noraz N, et al. Characterization of a Subtype of Autoimmune Encephalitis With Anti-Contactin-Associated Protein-like 2 Antibodies in the Cerebrospinal Fluid, Prominent Limbic Symptoms, and Seizures. *JAMA neurology* 2016;73(9):1115-1124.
26. Vincent A, Pettingill P, Pettingill R, et al. Association of Leucine-Rich Glioma Inactivated Protein 1, Contactin-Associated Protein 2, and Contactin 2 Antibodies With Clinical Features and Patient-Reported Pain in Acquired Neuromyotonia. *JAMA neurology* 2018;75(12):1519-1527.
27. Gadoth A, Pittock SJ, Dubey D, et al. Expanded phenotypes and outcomes among 256 LGI1/CASPR2-IgG-positive patients. *Annals of neurology* 2017;82(1):79-92.
28. Muniz-Castrillo S, Joubert B, Elsensohn MH, et al. Anti-CASPR2 clinical phenotypes correlate with HLA and immunological features. *Journal of neurology, neurosurgery, and psychiatry* 2020;91(10):1076-1084.
29. van Sonderen A, Thijs RD, Coenders EC, et al. Anti-LGI1 encephalitis: Clinical syndrome and long-term follow-up. *Neurology* 2016;87(14):1449-1456.
30. Durr M, Nissen G, Suhs KW, et al. CSF Findings in Acute NMDAR and LGI1 Antibody-Associated Autoimmune Encephalitis. *Neurology(R) neuroimmunology & neuroinflammation* 2021;8(6).
31. Geschwind MD, Tan KM, Lennon VA, et al. Voltage-gated potassium channel autoimmunity mimicking creutzfeldt-jakob disease. *Archives of neurology* 2008;65(10):1341-1346.
32. Tan KM, Lennon VA, Klein CJ, Boeve BF, Pittock SJ. Clinical spectrum of voltage-gated potassium channel autoimmunity. *Neurology* 2008;70(20):1883-1890.

676 **Tables and Figure legends**677 **Table 1**

	CASPR2-cohort	CASPR2/ LGI1-cohort	LGI1-cohort	p-value
n	149	15	105	
Gender f:m (% male)	17:132 (88·6)	3:12 (80)	46:59 (56)	<0·001
Age at onset, y, median (IQR; range)	68 (60-70; 20-85)	58 (48-65; 41-78)	65 (55-71; 22-86)	0·4
Syndrome, n (%)				
Definite limbic encephalitis [§]	93/149 (62·4)	1/15 (7)	90/105 (86)	<0·001
Definite autoimmune encephalitis [§]	3/149 (2·0)	0/15 (0)	12/105 (11)	0·002
Morvan syndrome	21/149 (14·1)	12/15 (80)	1/105 (1)	<0·001
Neuromyotonia	18/149 (12·1)	2/15 (13)	0/105 (0) *	<0·001
Isolated cerebellar syndrome	6/149 (4·0)	0/15 (0)	0/105 (0)	0·1
Isolated myoclonus	2/149 (1·3)	0/15 (0)	0/105 (0)	0·6
Others [§]	6/149 (4·0)	0/15 (0)	2/105 (2)	0·7
Clinical symptoms, n (%)				
Dyscognitive symptoms	108/146 (74·0)	5/15 (33)	90/101 (89)	<0·001
Psychiatric symptoms	78/144 (54·2)	9/15 (60)	52/101 (52)	0·8
Autonomic symptoms	47/141 (33·3)	13/15 (87)	11/100 (11)	<0·001
Epileptic seizures	104/148 (70·3)	4/15 (27)	82/104 (79)	<0·001
FBDS	0/149 (0·0)	0/15 (0)	26/105 (25)	<0·001
Sleep disorder	52/143 (36·4)	13/15 (87)	25/96 (26)	<0·001
Cerebellar symptoms	38/149 (25·5)	6/15 (40)	0/103 (0) *	<0·001
Movement disorders, n (%)				
Single movement disorder	44/149 (29·5)	4/15 (27)	4/105 (4) *	<0·001
Mixed movement disorder	9/149 (6·0)	7/15 (47)	0/105 (0)	<0·001
Gait ataxia	31/149 (20·8)	6/15 (40)	0/105 (0) *	<0·001
Myoclonus	15/149 (10·1)	9/15 (60)	0/105 (0)	<0·001
Chorea	4/149 (2·7)	1/15 (7)	2/105 (2)	0·5
Tics	0/149 (0·0)	0/15 (0)	0/105 (0)	-
Dystonia	0/149 (0·0)	0/15 (0)	0/105 (0)	-
Tremor	12/149 (8·1)	6/15 (40)	2/105 (2)	<0·001
Parkinsonism	2/149 (1·3)	0/15 (0)	0/105 (0)	0·6

678 **Table 1** Clinical characteristics of the CASPR2-, CASPR2/LGI1-double positive and LGI1-
679 cohort. P-values indicate significance on overall Fisher Exact test and bold script in individual
680 columns indicates significant results on post-hoc testing (see supplemental Table 1).
681 §According to Graus et al. 2016⁸. Others[§] n=1 isolated FBDS and n=1 generalized chorea in
682 the LGI1-cohort; n=2 brainstem encephalitis, n=2 generalized chorea, n=1 combined
683 myoclonus syndrome and n=1 epilepsy in the CASPR2-cohort *Post-hoc testing significant
684 between LGI1- and CASPR2/LGI1-cohort but not CASPR2 and CASPR2/LGI1-cohorts.
685 f=female, m=male, y=years, IQR=interquartile range, FBDS= facio-brachial dystonic
686 seizures.

687

688 **Table 2**

	CASPR2-cohort	CASPR2/LGI1-cohort	LGI1-cohort	p-value
n	149	15	105	
Diagnostic findings				
CSF pleocytosis (>5 cells) n (%)	39/104 (37·5)	1/12 (8)	13/94 (14)	<0·001
Elevated CSF total protein (>0·5g/l) n (%)	38/101 (37·6)	2/12 (17)	25/93 (27)	0·2
Isolated oligoclonal bands in CSF n (%)	15/65 (23·1)	0/9 (0)	6/92 (7)	0·006
CASPR2-aab positivity in CSF n (%)	89/97 (91·8)	5/14 (36)	0/56 (0)	<0·001
LGI1-aab positivity in CSF n (%)	0/97 (0·0)	3/14 (21)	42/56 (75)	<0·001
MRI suggestive of LE [§]	42/98 (42·9)	1/15 (7)	70/97 (72)	<0·001
Abnormal EEG	53/96 (55·2)	4/8 (50)	69/95 (73)	0·03
Underlying tumour	21/149 (14·1)	13/15 (87)	2/105 (2)	<0·001
Thymoma	9/149 (6·0)	12/15 (80)	0/105 (0·0)	<0·001
Other tumours	12/149 (8·1)	1/15 (7)	2/105 (2)	0·09
Treatment and outcome				
mRS at peak of disease median (IQR; range)	3 (2·3; 0·6)	4 (3·4; 2·6)	3 (2·3; 1·5))	0·006
mRS at last follow-up median (IQR; range)	1·5 (1·2; 0·6)	1 (1·2·5; 0·6)	1 (1·2; 0·6)	0·9
Follow up, n, median (IQR; range)	47 (18·50; 1·168)	47 (17·47; 6·47)	6 (2·21; 1·96)	<0·001
Steroids	102/145 (70·3)	12/14 (86)	100/105 (95)	<0·001
ivIG	56/145 (38·6)	14/14 (100)	26/105 (25)	<0·001
Plasmapheresis/immunadsorption	30/145 (20·7)	6/14 (43)	51/105 (49)	<0·001
Rituximab	34/145 (23·4)	6/14 (43)	25/105 (24)	0·3
Other immunosuppressants*	41/145 (28·3)	4/14 (29)	24/105 (23)	0·18

689 **Table 2** Diagnostic findings, treatment and outcome of patients with CASPR2-,
690 CASPR2/LGI1 and LGI1-aabs positivity in serum. P-values indicate significance on overall
691 Fisher Exact test and bold script in individual columns indicates significant results on post-
692 hoc testing (see supplemental Table 2). MRI= magnetic resonance imaging, EEG=
693 electroencephalography, mRS= modified ranking scale, IVIG= intravenous
694 immunoglobuline. [§] Uni- or bilateral medial temporal lobe abnormalities on FLAIR/T2.
695 *Other immunosuppressants included Mycophenolate mofetil, azathioprine,
696 cyclophosphamide, methotrexate, tocilizumab, see supplemental table 2 for details.
697

698 **Table 3**

All patients with CASPR2-aabs: Combined CASPR2- and CASPR2/LGI1 cohorts			
	Without Myoclonus	With myoclonus	p-value
n	140	24	
Gender f:m (% male)	18/122 (87.1)	2/22 (92)	0.7
Age at onset, y, median (IQR; range)	68 (60-69; 20-85)	64 (56-71; 41-81)	0.5
Syndrome and symptoms, n (%)			
Limbic encephalitis, n (%)	89/140 (63.6)	5/24 (21)	<0.001
Morvan syndrome, n(%)	21/140 (15.0)	12/24 (50)	0.001
Isolated myoclonus, n(%)	0/140 (0.0)	2/24 (8)	0.02
Autonomic symptoms	46/132 (34.8)	14/24 (58)	0.04
Epileptic seizures	99/139 (71.2)	9/24 (38)	0.002
Sleep disorder	50/134 (37.3)	15/24 (63)	0.03
Movement disorders, n (%)			
Single movement disorder	40/140 (28.6)	24/24 (100)	<0.001
Mixed movement disorder	36/140 (25.7)	12/24 (50)	0.03
Gait ataxia	4/140 (2.8)	12/24 (50)	<0.001
Chorea	28/140 (20.0)	9/24 (38)	0.07
Tremor	4/140 (2.9)	1/24 (4)	0.6
Parkinsonism	10/140 (7.1)	8/24 (33)	0.001
	2/140 (1.4)	0/24 (0)	1
Diagnostic findings			
LGI1-aab positivity in serum, n (%)	6/140 (4.3)	9/24 (38)	<0.001
CASPR2-aab positivity in CSF n (%)	82/91 (90.1)	12/20 (60)	0.03
MRI suggestive of LE [§]	41/92 (44.6)	2/21 (10)	0.003
Underlying tumour	24/138 (17.4)	10/24 (42)	0.01
Thymoma	12/138 (8.7)	9/24 (38)	0.001
Other tumours	12/138 (8.7)	1/24 (4)	0.7
Treatment and outcome			
mRS at peak of disease median (IQR; range)	3 (2.3; 0.6)	3 (3.4; 1.5)	0.002
mRS at last follow-up median (IQR; range)	1.5 (1.2; 0.6)	1 (1.2.75; 0.6)	0.9
Follow up, n, median (IQR; range)	47 (17-50; 1-168)	42 (14-47; 1-50)	0.1
Steroids	97/135 (71.9)	17/24 (71)	1
IVIg	51/135 (37.8)	19/24 (79)	<0.001
Plasmapheresis/immunadsorption	28/135 (20.7)	8/24 (33)	0.2
Rituximab	33/135 (24.4)	7/24 (29)	0.6
Other immunosuppressants*	46/135 (40.0)	10/24 (42)	1

Table 3: Relevant clinical characteristics, diagnostic findings and outcome of patients with positive CASPR2-aabs and prominent myoclonus compared to patients without myoclonus. CSF= cerebrospinal fluid, OCB= oligoclonal bands, MRI= magnetic resonance imaging, EEG= electroencephalography, mRS= modified ranking scale, IVIG= intravenous immunoglobuline. [§] Uni- or bilateral medial temporal lobe abnormalities on FLAIR/T2. *Other immunosuppressants included Mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate, tocilizumab, see supplemental table 4 for details on further examined non-significant characteristics and other immunosuppressants.

708
709

710

711

712

713

714 **Figure legends:**

715 **Figure 1:** Flow chart demonstrating the total number of patients included for this study and
716 the numbers in relation to the three different patient cohorts.

717 **Figure 2:** Modified Venn-diagrams showing the number of patients with single and combined
718 movement disorders and FBDS according to aab-defined cohorts.

719 **Figure 3:** Different clinical types of myoclonus in the context of CASPR2-autoimmunity.
720 Others*: n=2 brainstem encephalitis, n=1 combined myoclonus syndrome

721 **Figure 4:** Compound images of patients with paroxysmal segmental myoclonus of the lower
722 limbs. Stills of 4 patients included in this series are shown. All patients presented with
723 recurrent short-lasting attacks of myoclonus of the lower limbs triggered by orthostatism (A-
724 C) or walking (D) accompanied with severe gait unsteadiness. Patient videos are available in
725 the online supplemental data.

726

727

728 **Video legend:**

729 Video 1 Autoimmune episodic ataxia:

730 Patient 1 65-year-old male patient with recurrent paroxysmal episodes of gait and limb ataxia
731 and slurred speech. Such episodes occurred up to 8 times a day and lasted 1 to 2 minutes and
732 were triggered by orthostatism.

733

734

735 Video 2 Continuous spinal segmental myoclonus:

736 Patient 1 69-year-old male patient with CASPR2-associated isolated segmental spinal
737 myoclonus of the abdominal muscles with a burst duration of 300-400ms with a frequency of
738 1-2hz (Supplemental figure 1: Surface electromyography recordings). Treatment with
739 prednisolone and azathioprine resulted in complete alleviation of myoclonus.

740 Patient 2 77-year-old male patient with CASPR2-associated segmental spinal myoclonus of
741 the abdominal muscles and proximal lower limbs combined with camptocormia, head drop,
742 mild cognitive decline and progressive weakness of the upper limbs. Treatment with IVIG
743 resulted in marked improvement of myoclonus and further symptoms.

744

745

746 Video 3 Paroxysmal orthostatic segmental myoclonus of the lower limbs:

Patient 1: 53-year-old male patient with paroxysmal orthostatic segmental myoclonus of the lower limbs in the setting of Morvan syndrome. Attacks occurred multiple times per day with a duration of 10-15 seconds and were triggered by orthostatism and walking.

Patient 2 Paroxysmal myoclonus of the left leg triggered by orthostatism in a 72-year-old male patient with CASPR2-associated brainstem encephalitis with additional fluctuating complex extraocular palsy, anarthria and ataxia.

Patient 3: 68-year-old male patient with recurrent attacks of paroxysmal segmental myoclonus of the lower limbs triggered by orthostatism in the setting of Morvan syndrome. Attacks had a duration of 15-30 seconds and resulted in severe unsteadiness. Initially the patient was misdiagnosed as suffering from a functional movement disorder.

Patient 4 55-year-old male patient with paroxysmal segmental myoclonus of the lower limbs triggered by walking lasting for 10-15 seconds. Beside myoclonus the patient suffered from dysarthria with intermittent episodes of speech arrest and one generalized epileptic seizure occurred during the course of the disease. Initially the patients was misdiagnosed as suffering from a functional movement disorder.

Supplemental material:

Supplemental methods: Antibody testing strategies of participating laboratories.

Supplemental table1 : Biographic and clinical data of the total cohort with details on posthoc testing.

Supplemental table 2: Diagnostic findings, treatment and outcome of patients with CASPR2-, CASPR2/LGI1 and LGI1-aab positivity in serum with details on posthoc testing.

Supplemental table 3: Biographic and clinical data of CASPR2 and CASPR2/LGI1 antibody positive patients with and without ataxia

Supplemental table 4: Biographic and clinical data of CASPR2 and CASPR2/LGI1 antibody positive patients with and without myoclonus (full data set).

Supplemental table 5: Biographic and clinical data of CASPR2 and CASPR2/LGI1 antibody positive patients with and without tremor

Supplemental figure 1: Surface electromyography recordings showing spinal segmental myoclonus.