Frequency and Characterization of Movement Disorders in Anti-IgLON5 Disease

Carles Gaig, MD, PhD,* Yaroslau Compta, MD, PhD, Anna Heidbreder, MD, Maria J. Marti, MD, PhD, Maarten J. Titulaer, MD, PhD, Yvette Crijnen, MD, Birgit Hög, MD, Jan Lewerenz, MD, Maria Elena Erro, MD, PhD, Juan Carlos García-Moncó, MD, PhD, Pasqualine Ngro, MD, Nicola Tambascio, MD, Maja Patalong-Ogiwara, MD, Marcus Erdler, MD, Stefan Machner, MD, Evelyn Berger-Sieczkowski, MD, PhD, Romana Höflberger, MD, Christian Geis, MD, Markus Hutterer, MD, Angela Milán-Tomás, MD, Antonio Martín-Bastida, MD, Lydia Lopez Manzanares, MD, Sonia Quintas, MD, Günter U. Höglinger, MD, Nora Möhn, MD, Florian Schöbler, MD, Franziska S. Thaler, MD, Gian Maria Asioli, MD, Federica Provini, MD, PhD, Giuseppe Pazzi, MD, PhD, Koldo Berganzo, MD, Morten Blaabjerg, MD, Norbert Brüggemann, MD, Tarsis Farias, MD, Chen Fei Ng, MD, Caroline Giordana, MD, Federico Provini, MD, PhD, Giuseppe Pazzi, MD, PhD, Koldo Berganzo, MD, Morten Blaabjerg, MD, Norbert Brüggemann, MD, Tarsis Farias, MD, Chen Fei Ng, MD, Caroline Giordana, MD, Alejandro Herrero-San Martín, MD, Lucio Huebra, MD, Katya Kotschet, MD, Herbert Liendl, MD, Teresa Montoyo, MD, Carlos Morata, MD, Jesus Pérez-Pérez, MD, Inmaculada Puertas, MD, PhD, Thomas Seifert-Heid, MD, Caspar Seitz, MD, Mateus Mistieri Simabukuro, MD, Nieves Téllez, MD, Javier Villacieros-Álvarez, MD, Barbara Willekens, MD, Lidia Sabater, PhD, Alex Iranzo, MD, PhD, Joan Santamaria, MD, PhD, Josep Dalmau, MD, PhD, and Francesc Graus, MD, PhD*

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Abstract

Background and Objectives

Anti-IgLON5 disease is a recently described neurologic disease that shares features of autoimmunity and neurodegeneration. Abnormal movements appear to be frequent and important but have not been characterized and are underreported. We describe the frequency and types of movement disorders in a series of consecutive patients with this disease.

Methods

In this retrospective, observational study, the presence and phenomenology of movement disorders were assessed with a standardized clinical questionnaire. Available videos were centrally reviewed by 3 experts in movement disorders.

Results

Seventy-two patients were included. In 41 (57%), the main reason for initial consultation was difficulty walking along with one or several concurrent movement disorders. At the time of anti-
Several reviews have addressed the movement disorders of IgLON5 disease.63 (87%) patients had at least 1 movement disorder with a median of 3 per patient. The most frequent abnormal movements were gait and balance disturbances (52 patients [72%]), chorea (24 [33%]), bradykinesia (20 [28%]), dystonia (19 [26%]), abnormal body postures or rigidity (18 [25%]), and tremor (15 [21%]). Other hyperkinetic movements (myoclonus, akathisia, myorhythmia, myokymia, or abdominal dyskinesias) occurred in 26 (36%) patients. The craniofacial region was one of the most frequently affected by multiple concurrent movement disorders (23 patients [32%]) including dystonia (13), myorhythmia (6), chorea (4), or myokymia (4). Considering any body region, the most frequent combination of multiple movement disorders consisted of gait instability or ataxia associated with craniofacial dyskinesias or generalized chorea observed in 31 (43%) patients. In addition to abnormal movements, 87% of patients had sleep alterations, 74% bulbar dysfunction, and 53% cognitive impairment. Fifty-five (76%) patients were treated with immunotherapy, resulting in important and sustained improvement of the movement disorders in only 7 (13%) cases.

Discussion
Movement disorders are a frequent and leading cause of initial neurologic consultation in patients with anti-IgLON5 disease. Although multiple types of abnormal movements can occur, the most prevalent are disorders of gait, generalized chorea, and dystonia and other dyskinesias that frequently affect craniofacial muscles. Overall, anti-IgLON5 disease should be considered in patients with multiple movement disorders, particularly if they occur in association with sleep alterations, bulbar dysfunction, or cognitive impairment.

Anti-IgLON5 disease is a neurologic disorder associated with antibodies against IgLON5, a neuronal cell adhesion protein of unknown function.1 Most patients develop a combination of sleep alterations (non-REM and REM sleep parasomnias with stridor and obstructive sleep apnea), bulbar dysfunction (dysarthria, dysphagia, vocal cord palsy, or episodes of respiratory failure), and gait difficulties.2 Initial autopsy studies showed deposits of phosphorylated tau protein predominantly involving neurons of the tegmentum of the brainstem, suggesting a primary neurodegenerative disease.3 However, there is a strong association with the human leukocyte antigen (HLA) haplotype DRB1*10:01-DQB1*05:01, which is present in ~60% of patients (compared to 2% in the general population)3 and recent autopsy studies demonstrated absence of abnormal deposits of tau.4,5 Cultures of live neurons treated with IgLON5 antibodies showed an irreversible loss of surface IgLON5 clusters accompanied by changes in the cytoskeleton such as dystrophic neurites and axonal swellings.6,7 Taken together, these studies suggest that an antibody-mediated disruption of IgLON5 function leads to cytoskeletal alterations that could potentially result in tau accumulation.

Several reviews have addressed the movement disorders of different types of autoimmune encephalitis5,9 but for anti-IgLON5 disease the associated abnormal movements are less known or only partially described due to its more recent discovery. Although the sleep manifestations contributed to the identification of anti-IgLON5 disease,1 many patients develop movement disorders that precede the sleep dysfunction or are the reason for initial consultation, often suspecting initial symptoms of progressive supranuclear palsy (PSP).10,13 We describe the frequency, spectrum, and phenomenology of movement disorders in patients with anti-IgLON5 disease and provide clinical clues that may help in its diagnosis.

Methods

Patients and Clinical Evaluation
We retrospectively reviewed the clinical information of all patients with IgLON5 antibodies consecutively identified at the Neuroimmunology Laboratory of the Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), Hospital Clinic (Barcelona, Spain), from January 2014 to August 2020. The sleep dysfunction and general clinical features of 31 patients have been reported,1,2,5,10,11,14-22 but the abnormal movements were previously described in detail in only 3 of them.11,16,22

Initial Clinical Evaluation
Demographic and clinical data of the patients were provided by the referring physicians through a structured written questionnaire obtained by the time of IgLON5 antibody detection.2 Patients were classified into 1 of 5 clinical phenotypes according to the most predominant symptoms2,23-25: (1) sleep disorder; (2) bulbar syndrome; (3) movement disorders; (4) cognitive impairment; and (5) neuromuscular manifestations with muscle weakness, atrophy, or fasciculations.

Assessment of the Movement Disorders
The presence and types of movement disorders at the time of diagnosis were specifically assessed in all patients with a
second standardized questionnaire. In this questionnaire (eQuestionnaire available in Dryad [doi.org/10.5061/dryad.000000040]), the referring neurologists were asked to provide a complete description of the movement disorders and, if available, video recordings of the patients. Eighteen (40%) of 45 referring neurologists were movement disorders specialists and examined 32 (44%) patients. For each movement disorder, we specifically determined (1) the location, (2) if it was the main reason for the initial consultation, (3) if it was a predominant symptom at the time of anti-IgLON5 diagnosis, and (4) the response to immunotherapy independently of the observed response after symptomatic treatment.

Videos demonstrating the abnormal movements were available for 39 (54%) patients and were centrally reviewed in the hospital clinic by 3 specialists in movement disorders (Y. Compta, C. Gaig, M.J.M.) who classified them according to their phenomenology and information provided by the referring physicians. In patients with gait and balance disorders, we obtained the frequency of falls and whether there was impairment of postural reflexes assessed with the pull test according to the Movement Disorders Society–Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part III item. The gait disorder was defined as secondary to instability and balance impairment, caused by an associated movement disorder (for example, dystonic, choreic, or parkinsonian gait), or as cerebellar ataxia. For patients with clinical features resembling PSP, the clinical features were initially assessed by the referring neurologists and later confirmed by the centralized review at the Hospital Clinic to ascertain if they fulfilled the Movement Disorder Society diagnostic criteria for PSP (MDS-PSP).

### Laboratory Investigations
IgLON5 antibodies were tested by immunohistochemistry on rat brain sections and confirmed by a cell-based assay (CBA) of HEK293 cells transfected with IgLON5, as reported. The same CBA technique served to determine the IgLON5 immunoglobulin G (IgG) subclass using fluorescein-labeled secondary antibodies specific for the 4 IgG subclasses (The Binding Site), as reported. HLA class II genotyping was performed as previously described.

### Statistical Analyses
Data are reported as median and range or number and percentage. To determine the significance of differences in the prevalence of symptoms, signs, and laboratory findings (discontinuous outcome: present vs absent) between patients with a PSP-like phenotype and patients with other clinical presentations, Fisher exact probability test was used. The nonparametric Mann-Whitney U test was used to compare quantitative variables. P values less than 0.05 were considered significant. All analyses were done with SPSS version 22.0 (SPSS, Inc.).

### Standard Protocol Approvals, Registrations, and Patient Consents
The Ethics Committee of the Hospital Clinic approved the study. All patients or proxies gave written informed consent.

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### Table 1 Demographic Data and Clinical Features of 72 Patients With IgLON5 Antibodies

| Variable                                      | N (%) or median (range) |
|-----------------------------------------------|-------------------------|
| Age at disease onset, y                       | 62 (42–91)              |
| Male                                          | 40 (56)                 |
| Chronic presentation (in >4 months)           | 55 (70)                 |
| Age at diagnosis, y                           | 66 (46–91)              |
| Time from onset to diagnosis, mo              | 36 (1–216)              |
| Concomitant autoimmune diseases²              | 6 (8)                   |
| History of cancer²                            | 7 (10)                  |
| Main complaints leading to consultation¹      |                         |
| Gait problems                                 | 29 (40)                 |
| Sleep disturbances                            | 23 (32)                 |
| Movement disorders¹                           | 19 (26)                 |
| Bulbar symptoms                               | 17 (24)                 |
| Cognitive problems                            | 13 (18)                 |
| Other¹                                        | 7 (10)                  |
| Clinical phenotypes at diagnosis              |                         |
| Movement disorders²                           | 27 (37)                 |
| Bulbar syndrome                               | 17 (24)                 |
| Cognitive disorder                            | 12 (17)                 |
| Sleep disorder                                | 11 (15)                 |
| Neuromuscular                                 | 5 (7)                   |
| Brain MRI¹                                    |                         |
| Normal or nonspecific changes                 | 58/70 (83)              |
| Brainstem atrophy                             | 6/70 (9)                |
| Cerebellar atrophy                            | 3/70 (4)                |
| Other abnormalities                            | 3/70 (4)                |
| CSF analysis¹                                 |                         |
| Normal                                        | 28/63 (44)              |
| Pleocytosis (>5 mononuclear cells/μL)         | 17/63 (27)              |
| High protein level (>45 mg/dL)                | 29/63 (46)              |
| Positive oligoclonal bands                    | 5/28 (18)               |

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¹ Factor VIII deficiency (1), erythema nodosum (1), polymyalgia rheumatica (1), thyroiditis (1), diabetes mellitus type 1 (1), hypothyroidism (1).
² Breast cancer (2), thyroid cancer (1), kidney carcinoma (1), gastrointestinal neuroendocrine tumor (1), adrenal adenoma and pulmonary nodules (1), bladder carcinoma (1).
³ 28 patients had >1 presenting symptom: 2 symptoms (20), 3 symptoms (8).
⁴ Chorea (9), facial/abdominal dyskinesias (6), rigidity/spasms (2), parkinsonism (2).
⁵ Fasciculations and weakness (3), oculomotor symptoms (3), neurogenic pain (1).
⁶ Motor neuron-like disease (4), painful polyneuropathy (1).
⁷ Brain MRI could not be performed in 2 patients; other abnormalities included exhibiting-like hyperintensities (1), hippocampal atrophy (1), and putaminal hyperintensity (1).
⁸ CSF analysis was not performed in 9 patients. Patients with lymphocytic pleocytosis had a median of 9 white blood cells/μL (range 6–72). Patients with elevated protein levels had a median value of 72.6 mg/dL (range 49–192).
for the storage and use of serum, CSF, and clinical information for research purposes. The referring neurologist obtained consent from the patients to anonymously describe their clinical features. An additional authorization was obtained for disclosure of videos included in this article.

Data Availability
Anonymized data not published within this article will be made available by request from any qualified investigator.

Results
General Clinical, Laboratory, and Immunologic Features
Among 79 patients consecutively identified since 2014, 72 had assessable demographic, clinical, and immunologic features and were finally included in the study (Table 1). The median age of the 72 patients at symptom onset was 62 years (range 42–91) and 40 (56%) were male. Symptoms started before age 50 in 3 (4%) patients, and in 55 (76%) symptoms progressed over months or years. The remaining 17 (24%) patients had a rapid presentation of symptoms resulting in substantial clinical deficits in less than 4 months.

The distribution of clinical phenotypes at the time of anti-IgLON5 diagnosis is shown in Figure 1. The most common was the movement disorder phenotype, which occurred in 27 (37%) patients. Brain MRI was normal or showed nonspecific findings in 58 (83%) of 70 patients, whereas mild brainstem or cerebellar atrophy was demonstrated in 9 (13%). The CSF examination showed mild pleocytosis or elevated protein concentration in 35 (56%) of 63 patients (Table 1). IgLON5 antibodies were detected in 100% of sera and 52 (90%) of 58 patients with available CSF. IgG4 was the predominant IgG subclass in 40 (64%) of 62 patients whereas only 10 (14%) had IgLON5 antibodies exclusively of IgG1 class. The HLA DRB1*10:01 allele was found in 36 (54%) of 66 patients and all but 1 also were DQB1*05:01 positive.

Frequency and Relevance of Movement Disorders in anti-IgLON5 Disease
A movement disorder was the main reason for the neurologic consultation in 41 (57%) patients. Gait or balance alterations were the initial complaint in 29 (40%) patients, and 19 (26%, 7 of them with concurrent complaints of gait problems) consulted for other abnormal movements: generalized chorea (9), facial or abdominal dyskinesias (6), spasms in the lower limbs (2), and parkinsonism (2) (Table 1). At diagnosis, 63 (87%) patients had at least 1 movement disorder, with a median of 3 per patient (range 1–9). In order of frequency, 52 (72%) patients had a gait or balance disorder, 24 (33%) chorea, 20 (28%) bradykinesia, 19 (26%) dystonia, 18 (25%) abnormal body postures or rigidity, and 15 (21%) tremor (Table 2). Other hyperkinetic movements (myoclonus, akathisia, myorhythmia, myokymia, or abdominal dyskinesias) occurred in 26 (36%) patients (Figure 2). The most common combinations of movement disorders, observed in 31 (43%) patients, were postural instability or gait ataxia associated with generalized chorea or craniofacial dyskinesias including cranial dystonia, myorhythmia, facial myokymia, or chorea limited to face (Figure 3).

By the time of the diagnosis of IgLON5 disease, movement disorders were the most severe clinical manifestations in 27 (37%) of 72 patients, 10 of them had gait and oculomotor abnormalities resembling PSP, and the other 17 showed other movement disorders: 7 had craniofacial (5) or abdominal (2) dyskinesias, 4 chorea, 4 cerebellar gait ataxia and limb dysmetria, 1 subacute parkinsonism (bilateral asymmetrical bradykinesia with rigidity, resting tremor, hypomimia, and hypophonia), and 1 leg muscles stiffness and cramps resembling stiff-person syndrome (Figure 1). Movement disorders almost never occurred in isolation, as they were frequently accompanied by sleep (87% of patients), bulbar (74%), or cognitive (53%) symptoms (Table 3). Immunotherapy was given to 55 (76%) of 72 patients with a total of 145 movement disorders. Sustained (>3 months) symptom improvement was noted in 7/55 (13%) patients and involved 14 (10%) of the 145 movement disorders without preference for any type of abnormal movement (eTable 1 available in Dryad [doi.org/10.5061/dryad.000000040]).
Table 2  Movement Disorders in 72 Patients With Anti-IgLON5 Disease

| Abnormal movement and associated features | N (%) |
|------------------------------------------|-------|
| Gait disorder                            | 52 (72) |
| Reason for consultation                  | 29 (40) |
| Major symptom*                           | 31 (43) |
| Type of gait disorder*                   |       |
| Disequilibrium                           | 20/52 (38) |
| Cerebellar ataxia                        | 17/52 (33) |
| Disequilibrium/ataxia                    | 9/52 (17) |
| Parkinsonian                              | 4/52 (8) |
| Choreic                                   | 2/52 (4) |
| Chorea                                    | 24 (33) |
| Reason for consultation                  | 9 (12) |
| Major symptom                            | 12 (17) |
| Topography                                |       |
| Limb                                      | 20/24 (83) |
| Facial                                    | 18/24 (75) |
| Axial (trunk, neck)                       | 11/24 (46) |
| Bradykinesia                              | 20 (28) |
| Reason for consultation                  | 2 (3) |
| Major symptom                            | 4 (6) |
| Rigidity                                  | 10/20 (50) |
| Rest tremor                               | 2/20 (10) |
| Gaze palsy                                | 15/20 (75) |
| Dystonia                                  | 19 (26) |
| Reason for consultation                  | 3 (4)* |
| Major symptom                            | 7 (10) |
| Topography†                               |       |
| Cranial                                   | 15/19 (79) |
| Limb                                      | 7/19 (37) |
| Trunk (abdomen)                           | 1/19 (5) |
| Abnormal body postures and rigidity       | 18 (25) |
| Reason for consultation                  | 2 (3)* |
| Major symptom                            | 5 (7) |
| Topography                                |       |
| Antecollis                                | 8/18 (44) |
| Trunk bended or flexed                    | 6/18 (33) |
| Limb rigidity/stiffness                   | 5/18 (28) |
| Tremor                                    | 15 (21) |

* Major symptom was defined as a prominent manifestation at the time of anti-IgLON5 diagnosis, as stated by the treating neurologist.
† Most patients presented a gait disorder that combined postural instability with other features (see text).
‡ Mandibular dystonia in 2 patients and trunk dystonia in 1.
§ Fifteen patients had cranial dystonia including oromandibular or lingual dystonia (7 patients), blepharospasm (5 patients), and cervical dystonia (3 patients). Seven patients had limb dystonia (in 3 with concomitant cranial dystonia).
¶ Muscle stiffness with spasms in 2.
∥ One patient consulted because rest tremor associated with motor slowness.
¶ Myorhythmia in 2 patients and abdominal dyskinesias in 1.

Table 2  Movement Disorders in 72 Patients With Anti-IgLON5 Disease (continued)

| Abnormal movement and associated features | N (%) |
|------------------------------------------|-------|
| Reason for consultation                  | 1 (1)* |
| Major symptom                            | 1 (1) |
| Type                                      |       |
| Action upper limb tremor                 | 13/15 (87) |
| Rest tremor                              | 2/15 (13) |
| Cephalic tremor                          | 2/15 (13) |
| Voice tremor                             | 1/15 (7) |
| Other hyperkinesias                      | 26 (36) |
| Reason for consultation                  | 3 (4)* |
| Major symptom                            | 10 (14) |
| Type                                      |       |
| Myoclonus                                | 9/26 (35) |
| Akathisia                                | 9/26 (35) |
| Myorhythmia                              | 6/26 (23) |
| Myokymia                                 | 4/26 (15) |
| Abdominal dyskinesia                     | 2/26 (8) |

Distinct Types of Movement Disorders

Gait and Balance Disorders

gait impairment occurred in 52 (72%) patients (Table 2). Five types of gait alterations were identified: (1) disequilibrium with postural instability and altered postural reflexes in 20 of 52 (38%) patients (Video 1); in 7 of them, the disequilibrium was combined with 1 or several gait abnormalities including choreic movements (4), freezing of gait (2), parkinsonian gait with slowness, shuffling, and reduced arm swing (2), and dystonia (1); (2) broad-based gait occurred in 17 (33%) patients and was defined as cerebellar gait ataxia because irregular stepping was present in 13 patients and limb dysmetria in 10 (Video 2); in 9 of these 17 patients, ataxic gait was combined with chorea (3), parkinsonian gait (3), dystonia (2), and freezing (1); 4 of the 17 patients presented with chronic progressive prominent cerebellar syndrome and the diagnosis of multiple system atrophy (MSA) was initially suspected but none of them developed parkinsonism, orthostatic hypotension, or other manifestations.
of dysautonomia; (3) combination of both disequilibrium with postural instability and a cerebellar ataxic gait occurred in 9 (17%) patients; (4) isolated parkinsonian gait occurred in 4 (8%) patients, manifesting with slow gait with shuffling and freezing; and (5) gait impairment due to choreic movements affected 2 (4%) patients.

Twenty-nine (56%) of 52 patients had recurrent falls, with a frequency of >1 per month in 17 patients. The severity of the gait disorder was defined as moderate (need of a device for safe walking) in 14 (27%) patients and severe (walking only possible with the assistance of another person, or wheelchair bound) in 8 (15%). The pull test was altered in 29 (72%) of 40 assessed patients, 16 rated as moderately or severely impaired. Among the 52 patients with gait disorders, 40 were treated with several types of immunotherapy and 22 (55%) showed various rates of improvement. However, of these 22 patients, only 1 (4.5%) had full recovery and another 2 (9%) had an important and sustained improvement (eTable 1 available in Dryad [doi.org/10.5061/dryad.00000040]).

**Chorea**
Twenty-four (33%) patients developed chorea that was generalized in 20/24 (83%) patients, affecting the limbs but also the face in 14, and trunk in 10 (Video 3). In the other 4 patients without limb chorea, choreic movements were limited to the face in 3 and with concomitant trunk involvement in 1 (Video 4). Cognitive impairment was observed in 10 patients suggesting Huntington disease and genetic testing in 7 of them was negative. In 10/24 (42%) patients, chorea was severe enough to interfere with activities of daily living. Chorea improved with tetrabenazine in 4 of 7 patients, and with neuroleptics (haloperidol, tiapride) in 2 of 3. Immunotherapy was given to 21 patients, and 9 (43%) showed some degree of improvement, although a complete response was only achieved in 2 (9.5%) (eTable 1 available in Dryad [doi.org/10.5061/dryad.00000040]).

**Bradykinesia**
Twenty (28%) patients developed bradykinesia, which was bilateral in 18 (asymmetrical in 6). Ten (50%) of these patients also had rigidity and 2 had resting tremor, leading to
initially suspect a parkinsonian syndrome. Other symptoms compatible with this diagnosis included hypomimia (10 patients), hypophonia (6), and parkinsonian gait with slowness or freezing (9, in 5 of them combined with disequilibrium or ataxia) (Video 5). In 1 patient, parkinsonism was the most prominent manifestation. This patient was a 58-year-old woman who developed a subacute asymmetrical bradykinesia with rigidity, resting tremor, hypomimia, and hypophonia nonresponsive to levodopa. Additional symptoms included insomnia and daytime sleepiness, dysarthria with vocal cord palsy, and mild cognitive impairment. She did not have dysautonomia or cerebellar signs, and the dopamine transporter (DAT) imaging showed bilateral and asymmetric reduction of tracer uptake.

Dopaminergic neuroimaging was performed in 10 patients, including 9 with DAT-SPECT and 1 with fluorodopa PET. Three patients with isolated bradykinesia had normal studies,
Table 3 Additional Symptoms, Besides Movement Disorders, at Diagnosis of Anti-IgLON5 Disease

| Symptom                                      | N (%)     |
|----------------------------------------------|-----------|
| Sleep problems                               | 63 (87)   |
| History of sleep breathing difficulties      | 49 (68)   |
| Obstructive sleep apnea in a sleep study     | 42/52 (81)|
| Stridor during sleep in v-PSG                | 20/38 (53)|
| Sleep behaviors and vocalizations in v-PSG   | 40 (56)   |
| Non-REM parasomnia in v-PSG                  | 26/38 (68)|
| REM sleep behavior disorder in v-PSGa        | 19/31 (61)|
| Insomnia (sleep onset or fragmentation)      | 39 (54)   |
| Excessive daytime sleepiness                 | 37 (51)   |
| Bulbar dysfunction                           | 53 (74)   |
| Dysphagia b                                  | 42 (58)   |
| Dysarthria                                   | 38 (53)   |
| Episodes of acute respiratory failurec       | 18 (25)   |
| Stridor during wakefulness                   | 11 (15)   |
| Vocal cord palsy on laryngoscopy             | 17/29 (59)|
| Oculomotor abnormalities                     | 45 (62)   |
| Gaze palsiesd                                | 27 (37)   |
| Abnormal saccades                            | 20 (28)   |
| Abnormal pursuit                             | 19 (26)   |
| Nystagmus                                    | 14 (19)   |
| Eyelid ptosis                                | 15 (21)   |
| Dysautonomia                                 | 38 (53)   |
| Urinary dysfunction (urgency and incontinence)| 21 (29)     |
| Spontaneous episodes of intense perspiration | 19 (26)   |
| Gastrointestinal problems (constipation, diarrhoea) | 7 (10)    |
| Cardiac dysfunction (arrhythmias, Takotsubo) | 5 (7)        |
| Orthostatic hypotension                      | 3 (4)     |
| Cognitive impairment                         | 38 (53)   |
| Dementia                                     | 15 (21)   |
| Confusional episodes (delirium)              | 13 (18)   |
| Neuromuscular                                | 10 (14)   |
| Fasciculations in limb muscles               | 10 (14)   |
| Muscle weakness/atrophy                      | 3 (4)     |

Abbreviation: v-PSG = video-polysomnography.

a Confirmed by v-PSG. REM sleep was not recorded in 7 patients.
b Dysphagia was accompanied with drooling or excess of saliva and oral secretions in 18 patients or severe weight loss (>10 Kg) in 6.
c Respiratory failure was related to central hypoventilation in 10 patients and obstruction with vocal cord palsy in 8. Eight patients needed tracheotomy.
d Gaze palsy involved vertical movements in 23 patients (upgaze: 12; downgaze: 2; both upward and downward: 9). Horizontal gaze palsy was present in 13 (to both sides in 10). Nine patients had both vertical and horizontal gaze palsy. Only 2 patients (1 with a cognitive subtype and another with a motor neuron like syndrome) had vertical gaze palsy with predominant downgaze involvement.

Dystonia

Nineteen patients (26%) developed dystonia. In 15, the dystonia involved craniofacial muscles resulting in oromandibular or lingual involvement (7 patients, 2 of them with painful episodes of mandibular spasms that resembled trismus and prevented from normal feeding), blepharospasm (5), and cervical dystonia (3). In 2 patients, the cranial dystonia was the most prominent neurologic alteration at diagnosis. In 1 patient with lingual dystonia, the presence of dystonic movements in the trunk and repetitive spasms in the abdomen, chest, and shoulders were the main reason for initial consultation (Video 6). Limb dystonia occurred in 7 patients (3 of them along with cranial dystonia), with predominating involvement of the hand and fingers. Unlike cranial dystonia, limb dystonia was never severe or the reason for initial consultation. Four patients were treated with botulinum toxin, with partial response in 3. One patient with cervical dystonia had partial improvement with tetrabenazine. Eighteen patients received immunotherapy, but only 7 (39%) showed improvement, which was significant and sustained in 2, both with limb dystonia.

Abnormal Body Postures and Limb Rigidity

Thirteen (18%) patients developed abnormal postures and 5 (7%) limb rigidity. Among the 13 patients with abnormal postures, 8 had antecollis (in 2 the neck was also flexed laterally), 3 lateral bending of the trunk with a tendency to lean towards 1 side, resembling a Pisa syndrome, 1 lateral bending and forward flexing of the trunk, and 1 had antecollis and lateral bending of the trunk (Videos 5 and 6). Partial improvement of these body posture abnormalities occurred in 3 out of 8 patients treated with immunotherapy.

Among the 5 patients with limb rigidity and stiffness, the legs were affected in all 5 and the upper limbs in 3. In 4 patients, the stiffness was associated with painful spasms, predominantly involving hands (2 cases), and legs and lower back (2 cases). Limb stiffness and spasms were the main reason for consultation in 2 patients, 1 of them initially suspected of stiff-person syndrome. In this patient, additional symptoms included fasciculations and hyperekplexia; all antibodies related to the stiff-person spectrum of symptoms (glycine receptor, GAD65, amphiphysin, DPPX) were negative, but the patient showed a dramatic and sustained response to IV immunoglobulins.

Tremor

Fifteen (21%) patients had tremor, 14 predominantly involving the upper limbs, and 1 manifesting only with tremulous voice. Among the 14 patients with limb tremor, 12 had action tremor, 1 resting tremor, and the other case had mixed but 7 (3 with isolated bradykinesia) had a reduced tracer uptake (6 bilateral asymmetric and 1 symmetric). Seven patients underwent dopaminergic treatment with no significant response (levodopa dose ranging from 400 to 1,000 mg daily). Among 15 patients with bradykinesia/parkinsonism treated with immunotherapy, 3 showed partial and transient improvement and only 1 had full recovery.
action-resting tremor. Resting tremor was asymmetric and associated with bradykinesia and rigidity in both patients. In only 2 patients the tremor limited activities of daily living. In addition to limb tremor, 2 patients had intermittent and low amplitude cephalic tremor. In 5 of 15 patients, immunotherapy only achieved a partial and transient improvement.

### Other Hyperkinetic Movement Disorders

Twenty-six (36%) patients had several different hyperkinetic movement disorders, which included:

1. Facial dyskinesias in 10 (14%) patients, defined as myorhythmia in 6 (Video 7) and myokymia in 4 (Video 8). Myorhythmia, characterized by rhythmic slow movements, was restricted to the tongue and other oral muscles and was the predominant complaint leading to consultation in 2 patients. Four of 8 patients had a partial improvement following immunotherapy (2 with myorhythmia and 2 with myokymia). When the presence of facial dyskinesias was combined with that of cranial dystonia or chorea limited to the face, the overall number of patients with at least 1 craniofacial movement disorder was 23 (32%) and in 5 of them represented the predominant manifestation (Table 2).

2. Myoclonus occurred in 9 (12%) patients, involving the arms in all cases, and the legs in 4. It was symmetrical, intermittent, spontaneous, and mild to moderate in amplitude. In only 4 patients, limb myoclonus interfered with normal movements and actions. In 6 out of 9 patients, myoclonus improved following immunotherapy, although it resolved in only 2.

3. Akathisia was diagnosed in 9 (12%) patients. It was generalized in 3, localized to the legs in 4, and to legs and abdomen in 2. Akathisia improved with voluntary movements and worsened with rest in 6 patients; however, only 2 patients described a clear evening/night worsening. In 5 patients, restless legs syndrome was suspected, but only 1 fulfilled diagnostic criteria for this disorder. Four patients received dopaminergic treatment but only the patient who met criteria for restless legs syndrome improved. Akathisia improved after immunotherapy in 3 of 7 patients (eTable 1 available in Dryad [doi.org/10.5061/dryad.000000040]).

4. Abdominal dyskinesias occurred in 2 (3%) patients; in 1, the severity of the symptoms led to initial consultation. The abdominal dyskinesias were rapid, broad-based and intermittent, resulting in a sudden flexion of the trunk. In 1 patient, symptoms improved with tizanidine (6 mg daily).

### Cases Resembling PSP

In 10 (14%) patients, the gait disorder combined with oculomotor abnormalities suggested the diagnosis of PSP. In 9, the clinical features resembled Richardson syndrome and in 1 corticobasal syndrome. In addition to the gait disorder, all patients had postural instability and frequent falls. The type of gait dysfunction was heterogeneous and complex including combinations of postural instability with slowness, shuffling, freezing or broad-based gait. Gaze palsy occurred in 9 patients, involving only vertical movements in 6, horizontal in 1, and both in 2. Among the 8 patients with vertical gaze palsy, upward gaze was impaired in all patients, while downward gaze was also affected in 6. In all these patients, the downward gaze limitation was mild or did not predominate over upward gaze palsy. All patients with a PSP-like phenotype had a chronic presentation and their diagnosis was substantially delayed compared with the other IgLON5 phenotypes (median time to diagnosis 96 vs 24 months, *p* = 0.03) (Table 4).

Five patients fulfilled the Movement Disorder Society diagnostic criteria for probable PSP, but the concurrent presence of other neurologic features, such as prominent sleep dysfunction and abnormal sleep behaviors (3), stridor with vocal cord palsy (2), episodes of respiratory failure (2), limb stiffness with spasms (1), or chorea (1), challenged the PSP diagnosis. In 5 patients, Movement Disorder Society criteria were not fulfilled because they had limb ataxia (3) or dysautonomia with orthostatic hypotension (3).

### Table 4 Characteristics of Patients With PSP-Like Phenotype Compared to Those With Other Phenotypes

|                      | PSP-like phenotype (n = 10) | Other phenotypes (n = 62) | p Value |
|----------------------|----------------------------|---------------------------|---------|
| Age at disease onset, y | 62 (44–71)                 | 63 (42–91)                | 0.74    |
| Sex, male            | 7 (70)                     | 33 (53)                   | 0.50    |
| Chronic onset        | 10 (100)                   | 45 (73)                   | 0.10    |
| Time to diagnosis, mo| 96 (24–216)                | 24 (1–180)                | 0.028   |
| Gait difficulties    | 10 (100)                   | 42 (68)                   | 0.053   |
| Oculomotor abnormalities | 10 (100)            | 35 (56)                   | 0.01    |
| Limb ataxia          | 3 (10)                     | 15 (24)                   | 0.70    |
| Chorea               | 1 (10)                     | 23 (37)                   | 0.15    |
| Bradykinesia         | 8 (80)                     | 12 (19)                   | <0.001  |
| Dystonia             | 5 (50)                     | 14 (23)                   | 0.12    |
| Sleep problems       | 10 (100)                   | 53 (85)                   | 0.30    |
| Bulbar dysfunction   | 7 (70)                     | 46 (74)                   | 0.70    |
| Dysautonomic symptoms | 9 (90)                     | 29 (47)                   | 0.015   |
| Orthostatic hypotension | 3 (30)                    | 0 (0)                     | 0.02    |
| Cognitive impairment | 7 (70)                     | 31 (50)                   | 0.30    |
| Brainstem atrophy on MRI | 4/10 (40)                | 2/60 (3)                  | 0.003   |
| IgLON5 antibodies in CSF | 4/8 (50)              | 48/50 (96)                | 0.002   |
| HLA DRB1*1001        | 1/6 (17)                   | 35/56 (62)                | 0.07    |

Abbreviation: PSP = progressive supranuclear palsy. Data are reported as median (range) or number (%).
One patient with a PSP-like phenotype had a corticobasal syndrome. He was a 61-year-old man with a 6-year history of progressive gait failure (with freezing and disequilibrium), vertical gaze palsy, cognitive decline with episodic memory and attention impairment, nonfluent aphasia, bilateral limb and orobuccal apraxia, asymmetric alien limb phenomenon, and a rigid-akinetic syndrome with mild finger myoclonus and bilateral grasping. Brain MRI showed generalized brain atrophy without significant asymmetries and he only had IgLON5 antibodies in serum (CSF negative). Symptoms did not improve with IV methylprednisolone and immunoglobulins.

Discussion

In this retrospective study of 72 consecutive patients with anti-IgLON5 disease, we show that 87% had abnormal movements, and in 57% the movement disorder was the main or initial reason for neurologic consultation. Most patients had multiple abnormal movements, with a median number of 3 per patient. Gait disturbances associated with craniofacial dyskinesias or generalized chorea were the most common combinations of movement disorders, observed in 31 (43%) patients. Although in 37% of patients, the movement disorders were a prominent clinical manifestation, they rarely occurred in isolation and usually associated with sleep, bulbar, or cognitive alterations, providing an important clue for the diagnosis.

Gait balance and postural disorders were the main reason for the first neurologic consultation in 40% of patients. The disturbance of gait and balance was heterogeneous and patients frequently had more than 1 alteration that contributed to the gait dysfunction. The most common finding was postural instability with frequent falls, sometimes associated with a broad-based gait similar to that seen during the course of PSP. A broad-based gait without postural instability occurred in 17/52 (33%) patients, and although this is not specific of a particular disorder, the association with an irregular step cadence and limb dysmetria made us classify it as cerebellar gait ataxia. In patients with a cerebellar syndrome combined with abnormal body postures or striidor, the differential diagnosis with MSA was often considered. However, severe autonomic failure, a key feature of MSA, rarely occurs in patients with anti-IgLON5 disease.

In 14% of patients, the combination of gait and balance disturbances, frequent falls, and gaze palsy with bradykinesia and rigidity were reminiscent of classical PSP. Compared with other anti-IgLON5 clinical phenotypes, patients with a PSP-like syndrome were diagnosed later in the course of the disease, suggesting that the diagnosis of anti-IgLON5 disease was less frequently considered at symptom onset. Although 5 out of 10 patients with a PSP-like phenotype fulfilled criteria of probable PSP, 2 clues were important for the diagnosis: (1) patients with anti-IgLON5 disease rarely have predominant downgaze involvement and (2) most patients with PSP-like phenotype had additional neurologic alterations that do not form part of classical PSP presentation.

Chorea was the second most common movement disorder. It occurred in one-third of the patients with anti-IgLON5 disease and was the reason for neurologic consultation in 12%. Even though there are no studies on prevalence, anti-IgLON5 disease is probably the most common cause of autoimmune chorea in the elderly as other types of autoimmune chorea, such as antiphospholipid syndrome and Sydenham chorea, typically affect younger patients. Other causes of autoimmune chorea in the elderly include paraneoplastic syndromes and less frequently anti-LGI1 or CASPR2 encephalitis. Paraneoplastic chorea usually associates with CRMP5 antibodies and lung cancer but it has also been described with other types of cancer without onconeural antibodies. Patients with paraneoplastic chorea frequently have weight loss and peripheral neuropathy, which are not part of the anti-IgLON5 phenotype manifesting with chorea. In some of our patients, the chronic development of chorea along with cognitive impairment, bradykinesia, dystonia, or oculomotor abnormalities suggested the diagnosis of Huntington disease but none showed caudate atrophy, which is a characteristic MRI feature of Huntington disease. In the clinical setting of chorea of unclear cause and severe sleep disruption, the diagnosis of anti-IgLON5 disease must be considered. Future studies should determine the prevalence of anti-IgLON5 antibodies in elderly patients with isolated or prominent generalized chorea.

Craniofacial dyskinesias occurred in 32% of patients with anti-IgLON5 disease, predominantly manifesting as dystonia and less frequently as myorhythmia, chorea, or myokymia. Facial dyskinesias, comprising chorea, dystonia, or stereotypies, are common in anti-NMDAR encephalitis, but this disease usually affects children and young adults and associates with a clearly different spectrum of symptoms. In later adulthood, another cause of immune-mediated oromandibular or cervical dystonia is paraneoplastic brainstem encephalitis in the context of breast cancer and Ri (ANNA2) antibodies. More, painful mandibular spasms, such as those observed in 2 of our patients, can also occur in patients with anti-Ri encephalitis and those with progressive encephalomyelitis with rigidity and myoclonus associated with glycine receptor antibodies.

Myorhythmia and myokymia were the second most common facial dyskinesia in our patients (14%). Myorhythmia is defined as a repetitive, rhythmic, slow frequency movement that affects cranial and limb muscles and sometimes is difficult to distinguish from myokymia. The myorhythmia in anti-IgLON5 cases did not involve the ocular muscles, as typically occurs in Whipple disease, and was more restricted to the tongue and oromandibular muscles. Facial myorhythmia has been described in some patients with anti-NMDAR encephalitis but not in other types of autoimmune encephalitis. The frequency of myorhythmia in anti-NMDAR encephalitis or anti-IgLON5 disease cannot be ascertained as it is frequently described with several phenomenologic terms when independently assessed by experts in movement disorders.
Although not the main aim of our study, we included in the questionnaire to physicians whether the movement disorders responded to immunotherapy independently of the effect of symptomatic treatment. Considering the limitations of this retrospective assessment, it is important to note that only a minority of patients appeared to have relevant and sustained improvement after immunotherapy. This is in line with previous series and single case reports, where immunotherapy was effective in only a few patients.18,23,30,47-49 The number of patients with apparent response to immunotherapy is too small to determine the factors that associated with improvement or the most effective treatments.19

Our series has the limitations of all retrospective studies where a consensus of phenomenologic terms to define movement disorders has not been established before clinical assessment; also, videos were not available from all patients, and when available, did not always capture all movement disorders. We did not assess the underlying factors that influence the expression of movement disorders and different clinical phenotypes in anti-IgLON5 disease, a task that will need to be considered in future studies. However, there is no patient selection bias given that all patients identified by the authors since the time anti-IgLON5 disease was discovered were included in the study. All patients were examined by at least 1 of the authors (40% of them movement disorders specialists) and information was collected following a systematic and standardized questionnaire.

The current findings provide several practical diagnostic clues and clinical implications: (1) movement disorders are common in anti-IgLON5 disease and are a frequent cause of initial consultation; (2) this disease should be suspected in patients presenting with a combination of multiple movement disorders without an alternative explanation; (3) gait and balance dysfunction along with craniofacial dyskinesias or generalized chorea are the most common combinations of movement disorders; (4) even though the movement disorders can be severe or predominant, they rarely occur in isolation and are usually accompanied by other clinical features of anti-IgLON5 disease such as sleep, bulbar, and cognitive deficits; (5) because the clinical presentation is often insidious and most patients do not have signs of inflammation in CSF or MRI studies, a high degree of clinical awareness is needed for the diagnosis of this disease50; and (6) a trial of immunotherapy is indicated as some patients show important and sustained clinical responses.

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Appendix Authors

| Name             | Location                                      | Contribution                                                                 |
|------------------|-----------------------------------------------|------------------------------------------------------------------------------|
| Carles Gaig, MD, PhD | Institut d’Investigacions Biomédiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data |
| Yaroslau Compta, MD, PhD | Department of Neurology, Hospital Clinic, Barcelona, Spain | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data |
| Name                  | Location                                                                 | Contribution                                                                                       |
|----------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Anna Heidbreder, MD  | Department Neurology, Division of Sleep Medicine and Neuromuscular Disorders, University Hospital Muenster, Germany | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data |
| Maria J Marti, MD, PhD| Department of Neurology, Hospital Clinic, Barcelona, Spain                | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data |
| Maarten J. Titulaer, MD, PhD | Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Yvette Crijnen, MD  | Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Birgit Högl, MD      | Department of Neurology, Medical University of Innsbruck, Austria          | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Jan Lewerenz, MD     | Department of Neurology, Ulm University, Germany                          | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Maria Elena Erro, MD, PhD | Neurology Department, Complejo Hospitalario de Navarra, Navarra Institute for Health Research (IdiSNA), Pamplona, Spain | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Juan Carlos Garcia-Moncó, MD, PhD | Neurology Department, Hospital Universitario de Basurto, Bilbao (formerly Department of Neurology, Hospital de Galdakao, Spain) | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Pasquale Nigro, MD   | Movement Disorders Center, Perugia General Hospital and University of Perugia, Italy | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Nicola Tambasco, MD  | Movement Disorders Center, Perugia General Hospital and University of Perugia, Italy | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Maja Patalong-Ogiewa, MD | Department of Neurology and Neurorehabilitation, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Marcus Erdler, MD     | Department of Neurology, Klinik Donaustadt, Karl-Landsteiner-Institut, Vienna, Austria | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Stefan Macher, MD     | Department of Neurology, Medical University of Vienna, Austria             | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Evelyn Berger-Sieczkowski, MD, PhD | Department of Neurology, Medical University of Vienna, Austria | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Romana Hoftberger, MD | Division of Neuropathology and Neurochemistry, Department of Neurology, Medical University of Vienna, Austria | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Christian Geis, MD    | Section Translational Neuroimmunology, Department of Neurology, Jena University Hospital, Germany | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Markus Hutterer, MD   | Department of Neurology 1, Neuromed Campus, Kepler Universitätshospital Linz, Austria | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Angela Milán-Tomás, MD | Department of Neurology and Neurosciences, Clínica Universidad de Navarra, Pamplona-Madrid, Spain | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Antonio Martin-Bastida, MD | Department of Neurology and Neurosciences, Clínica Universidad de Navarra, Pamplona-Madrid, Spain | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Lydia Lopez Manzanares, MD | Department of Neurology, Hospital La Princesa, Madrid, Spain | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Sonia Quintas, MD     | Department of Neurology, Hospital La Princesa, Madrid, Spain              | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Name                          | Location                                                                 | Contribution                                                                                     |
|-------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Günter U. Hoglinger, MD       | Department of Neurology, Hannover Medical School, Germany               | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Nora Möhn, MD                 | Department of Neurology, Hannover Medical School, Germany               | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Florian Schöberl, MD          | Department of Neurology, Ludwig-Maximilians-University, Munich, Germany | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Franziska S. Thaler, MD       | Institute of Clinical Neuroimmunology, University Hospital and Biomedical Center, Ludwig-Maximilians University Munich, Germany | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Gian Maria Asiol, MD          | Department of Biomedical and NeuroMotor Sciences (DiBiNeM), Alma Mater Studiorum University of Bologna, Bologna, Italy | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Federica Provin, MD, PhD      | Department of Biomedical and NeuroMotor Sciences (DiBiNeM), Alma Mater Studiorum University of Bologna, Italy | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Giuseppe Plazzi, MD, PhD      | Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Koldo Berganzo, MD            | Neurology Department, Cruces University Hospital, Barakaldo, Spain       | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Morten Blaabjerg, MD          | Department of Neurology, Odense University Hospital, Denmark            | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Norbert Bruggemann, MD        | Department of Neurology and Institute of Neurogenetics, University of Lubeck, Germany | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Tarsis Farias, MD             | Department of Neurology, Medical Clinic of Hospital Geral Cleriston Andrade, Feira de Santana, Brazil | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Chen Fei Ng, MD               | Neurology Unit, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Caroline Giordana, MD         | Department of Movement Disorders and Neurology, CHU Nice, France          | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Alejandro Herrero-San Martin, MD | Department of Neurology, Hospital Universitario 12 de Octubre, Madrid, Spain | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Lucio Huebra, MD              | Department of Psychobiology, Universidade Federal de São Paulo, Brazil   | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Katya Kotschet, MD            | Clinical Neurosciences, St Vincent's Hospital, Melbourne, Australia      | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Herburg Liendl, MD            | Department of Neurology, LKH Murtal, Standort Knittelfeld, Austria      | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Teresa Montejo, MD            | Department of Neurology, Fundacion Jimenez Diaz, Madrid, Spain          | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Carlos Morata, MD             | Department of Neurology, Hospital Universitari i Politècnic La Fe, Valencia, Spain | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Jesus Pérez-Pérez, MD         | Department of Neurology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Inmaculada Puertas, MD, PhD   | Department of Neurology, Hospital La Paz, Madrid, Spain                 | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Thomas Seifert-Held, MD       | Department of Neurology, Medical University of Graz, Austria            | Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
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