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Frequency and Characterization of Movement Disorders in Anti-IgLON5 Disease

Frequency and characterization of movement disorders in anti-IgLON5 disease

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Abstract

Objective: Anti-IgLON5 disease is a recently described neurological disease that shares features of autoimmunity and neurodegeneration. Abnormal movements appear to be frequent and important but have not been characterized and are under-reported. Here 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 three 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-IgLON5 diagnosis, 63 (87%) patients had at least one movement disorder with a median of three 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%) of 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 seven (13%) cases.

Conclusions: Movement disorders are a frequent and leading cause of initial neurological 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.

Introduction

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.[1] 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 encephalitis[8, 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] Here, 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 previously

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 one of five clinical phenotypes according to the most predominant symptoms:[2, 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) 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 disorder 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 three specialists in movement disorders (YC, CG, MJM) who classified them according to their phenomenology[26] 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 Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III item.[27] 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).[28]

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.[1] The same CBA technique served to determine the IgLON5-IgG subclass using fluorescein-labelled secondary antibodies specific for the four IgG subclasses (The Binding Site, Birmingham, England), as reported. [6] HLA class II genotyping was performed as previously described.[3]

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 (dichotomous outcome: present versus absent) between patients with a PSP-like phenotype and patients with other clinical presentations, Fisher exact probability test was used. The non-parametric Mann Whitney's 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., Chicago, IL).

Standard protocol approvals, registrations, and patient consents

The Ethic Committee of the Hospital Clinic approved the study. All patients or proxies gave written informed consent for the storage and use of serum, CSF, and clinical information for research purposes. 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 manuscript.

Data availability

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

Results

General clinical, laboratory, and immunological features

Among 79 patients consecutively identified since 2014, 72 had assessable demographic, clinical and immunological 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 the age of 50 in three (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 that occurred in 27 (37%) patients. Brain MRI was normal or showed non-specific findings in 58 (83%) of 70 patients, whereas mild brainstem or cerebellar atrophy was demonstrated in nine (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 53 (77%) of 69 patients whereas only 10 (14%) had IgLON5

antibodies exclusively of IgG1 class. The HLA DRB1*10:01 allele was found in 36 (58%) of 62

patients and all but one 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 neurological 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 one movement disorder with a median of three

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: seven had craniofacial (5) or

abdominal (2) dyskinesias; four chorea; four cerebellar gait ataxia and limb dysmetria; one subacute

parkinsonism (bilateral asymmetrical bradykinesia with rigidity, resting tremor, hypomimia and

hypophonia); and one 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 1available in Dryad).

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 seven of them, the disequilibrium was combined with one 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 nine of these 17 patients, ataxic gait was combined with chorea (3), parkinsonian gait (3), dystonia (2), and freezing (1). Four 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 nine (17%) patients; 4) isolated parkinsonian gait occurred in four (8%) patients, manifesting with slow gait with shuffling and freezing; and 5) gait impairment due to choreic movements affected two (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 eight (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 one (4.5%) had full recovery and another two (9%) had an important and sustained improvement (eTable 1 available in Dryad).

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 four patients without limb chorea, choreic movements were limited to the face in 3 and with concomitant trunk involvement in one (video 4). Cognitive impairment was observed in 10 patients suggesting Huntington disease and genetic testing in seven 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 four of seven patients, and with neuroleptics (haloperidol, tiapride) in two of three. Immunotherapy was given to 21 patients, and nine (43%) showed some degree of improvement, although a complete response was only achieved in two (9.5%) (eTable 1 available in Dryad).

Bradykinesia

Twenty (28%) patients developed bradykinesia, which was bilateral in 18 (asymmetrical in six). Ten (50%) of these patients also had rigidity and two 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 five of them combined with disequilibrium or ataxia) (video 5). In one patient, parkinsonism was the most prominent

manifestation. This patient was a 58 year-old female who developed a subacute asymmetrical bradykinesia with rigidity, resting tremor, hypomimia, and hypophonia non-responsive 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 nine with DAT- SPECT and one with fluorodopa positron emission tomography. Three patients with isolated bradykinesia had normal studies, but seven (three with isolated bradykinesia) had a reduced tracer uptake (six bilateral asymmetric, and one symmetric). Seven patients underwent dopaminergic treatment with no significant response (levodopa dose ranging from 400 to 1000 mg daily). Among 15 patients with bradykinesia/parkinsonism treated with immunotherapy, three showed partial and transient improvement and only one had full recovery.

Dystonia

Nineteen patients (26%) developed dystonia. In fifteen, the dystonia involved craniofacial muscles resulting in oromandibular or lingual involvement (7 patients, two of them with painful episodes of mandibular spasms that resembled trismus and prevented from normal feeding), blepharospasm (5) and cervical dystonia (3). In two patients, the cranial dystonia was the most prominent neurological alteration at diagnosis. In one 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 seven patients (three 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 three. One patient with cervical

dystonia had partial improvement with tetrabenazine. Eighteen patients received immunotherapy, but only seven (39%) showed improvement that was significant and sustained in two, both with limb dystonia.

Abnormal body postures and limb rigidity

Thirteen (18%) patients developed abnormal postures and five (7%) limb rigidity. Among the 13 cases with abnormal postures, 8 had antecollis (in two the neck was also flexed laterally), 3 lateral bending of the trunk with a tendency to lean towards one 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 three out of eight patients treated with immunotherapy.

Among the five patients with limb rigidity and stiffness, the legs were affected in all five and the upper limbs in three. In four 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 two patients, one of them initially suspected of stiff-person syndrome. In this patient additional symptoms included fasciculations and hyperekplexia; all antibodies related with stiff-person spectrum of symptoms (glycine receptor, GAD65, amphiphysin, DPPX)[8] were negative, but the patient showed a dramatic and sustained response to intravenous immunoglobulins.

Tremor

Fifteen (21%) patients had tremor, 14 predominantly involving the upper limbs, and 1 manifesting only with tremolous voice. Among the 14 patients with limb tremor, 12 had action tremor, 1 resting tremor, and the other case had mixed action-resting tremor. Resting tremor was asymmetric and associated with bradykinesia and rigidity in both patients. In only two patients the tremor limited

activities of daily living. In addition to limb tremor two patients had intermittent and low amplitude cephalic tremor. In five 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 six (video 7) and myokymia in four (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 two patients. Four of 8 patients had a partial improvement following immunotherapy (two with myorhythmia and two 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 one craniofacial movement disorder was 23 (32%) and in five of them represented the predominant manifestation (table 2).

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

3) Akathisia was diagnosed in nine (12%) patients. It was generalized in three, localized to the legs in four, and to legs and abdomen in two. Akathisia improved with voluntary movements and worsened with rest in six patients; however, only two patients described a clear evening-night worsening. In five patients restless legs syndrome was suspected but only one fulfilled diagnostic criteria for this disorder. Four patients received dopaminergic treatment but only the patient that met criteria for restless legs syndrome improved. Akathisia improved after immunotherapy in three of seven patients

(eTable 1 available in Dryad).

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

Patients resembling PSP

In 10 (14%) patients the gait disorder combined with oculomotor abnormalities suggested the diagnosis of PSP. In nine, the clinical features resembled the Richardson's syndrome and in one the corticobasal syndrome.[29, 30] 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 nine patients, involving only vertical movements in six, horizontal in one, and both in two. Among the eight patients with vertical gaze palsy, upward gaze was impaired in all patients, while downward gaze was also affected in six. 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 MDS diagnostic criteria for probable PSP, but the concurrent presence of other neurological features, such as prominent sleep dysfunction and abnormal sleep behaviours (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 five patients, MDS criteria were not fulfilled because they had limb ataxia (3) or dysautonomia with orthostatic hypotension (3).

One patient with a PSP-like phenotype had a corticobasal syndrome. He was a 61 year-old man with 6 years history of progressive gait failure (with freezing and disequilibrium), vertical gaze

palsy, cognitive decline with episodic memory and attention impairment, non-fluent aphasia, bilateral limb and orobuccal apraxia, asymmetrical 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 intravenous 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 neurological consultation. Most patients had multiple abnormal movements with a median number of three 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 neurological consultation in 40% of patients. The disturbance of gait and balance was heterogeneous and patients frequently had more than one 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.[31] A broad-based gait without postural instability occurred in 17/52 (33%) patients, and although this is not specific of a particular disorder,[32] 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 stridor the differential diagnosis with MSA was often considered. However, severe autonomic failure, a key

feature of MSA,[33] rarely occurs in patients with anti-IgLON5 disease.

In 14% of patients the combination of gait and balance disturbances, frequent falls, and gaze palsies 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 five out of 10 patients with a PSP-like phenotype fulfilled criteria of probable PSP two 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 neurological 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 neurological 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 since other types of autoimmune chorea, such as anti-phospholipid syndrome and Sydenham chorea, typically affect younger patients.[34] Other causes of autoimmune chorea in the elderly include paraneoplastic syndromes and less frequently anti-LGI1 or CASPR2 encephalitis.[34] Paraneoplastic chorea usually associates with CRMP5 antibodies and lung cancer but it has also been described with other types of cancer without onconeural antibodies.[35] Patients with paraneoplastic chorea frequently have weight loss and peripheral neuropathy which are not part of the anti-IgLON5 phenotype manifesting with chorea.[36] 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.[37] In the clinical setting of chorea of unclear cause and severe sleep disruption, the diagnosis of anti-IgLON5 disease must be

considered.[10, 38, 39] 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.[40] 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.[41] Moreover, painful mandibular spasms such as those observed in two of our patients, can also occur in patients with anti-Ri encephalitis and those with progressive encephalomyelitis with rigidity and myoclonus (PERM) associated with glycine receptor antibodies.[41, 42]

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.[43] The myorhythmia in anti-IgLON5 patients did not involve the ocular muscles, as typically occurs in Whipple's disease,[44] and was more restricted to the tongue and oromandibular muscles.[12, 23, 45] Facial myorhythmia has been described in some patients with anti-NMDAR encephalitis but not in other types of autoimmune encephalitis.[8, 9, 43] The exact frequency of myorhythmia in anti-NMDAR encephalitis or anti-IgLON5 disease cannot be ascertained since it is frequently described with several phenomenological terms when independently assessed by experts in movement disorders.[40, 46]

Although it was 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, 39, 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 phenomenological terms to define movement disorders has not been pre-established before clinical assessment; 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 clinic 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 one of the authors (40% of them movement disorder specialists) and information was collected following a systematic and standardized questionnaire.

Overall, 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 disease,[50] and 6) a trial of immunotherapy is indicated as a few patients show important and sustained clinical responses.

References

1.   Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol 2014;13:575-586.

2.   Gaig C, Graus F, Compta Y, et al. Clinical manifestations of the anti-IgLON5 disease. Neurology 2017;88:1736-1743.

3.   Gaig C, Ercilla G, Daura X, et al. HLA and microtubule-associated protein tau H1 haplotype associations in anti-IgLON5 disease. Neurol Neuroimmunol Neuroinflamm 2019;6:e605.

4.   Cagnin A, Mariotto S, Fiorini M, et al. Microglial and Neuronal TDP-43 Pathology in Anti-IgLON5-Related Tauopathy. Journal of Alzheimer's disease : JAD 2017;59:13-20.

5.   Erro ME, Sabater L, Martinez L, et al. Anti-IGLON5 disease: A new case without neuropathologic evidence of brainstem tauopathy. Neurol Neuroimmunol Neuroinflamm 2020;7:e651.

6.   Sabater L, Planaguma J, Dalmau J, Graus F. Cellular investigations with human antibodies associated with the anti-IgLON5 syndrome. J Neuroinflammation 2016;13:226.

7.   Landa J, Gaig C, Planagumà J, et al. Effects of IgLON5 antibodies on neuronal cytoskeleton: a link between autoimmunity and neurodegeneration. Ann Neurol 2020;88:1023-1027.

8.   Balint B, Vincent A, Meinck HM, Irani SR, Bhatia KP. Movement disorders with neuronal antibodies: syndromic approach, genetic parallels and pathophysiology. Brain 2018;141:13-36.

9.   Baizabal-Carvallo JF, Jankovic J. Autoimmune and paraneoplastic movement disorders: An update. J Neurol Sci 2018;385:175-184.

10.   Simabukuro MM, Sabater L, Adoni T, et al. Sleep disorder, chorea, and dementia associated with IgLON5 antibodies. Neurol Neuroimmunol Neuroinflamm 2015;2:e136.

11.   Bruggemann N, Wandinger KP, Gaig C, et al. Dystonia, lower limb stiffness, and upward gaze palsy in a patient with IgLON5 antibodies. Mov Disord 2016;31:762-764.

12.   Morales-Briceno H, Cruse B, Fois AF, et al. IgLON5-mediated neurodegeneration is a differential diagnosis of CNS Whipple disease. Neurology 2018;90:1113-1115.

13.   Gaig C, Compta Y. Neurological profiles beyond the sleep disorder in patients with anti-IgLON5 disease. Curr Opin Neurol 2019;32:493-499.

14.   Hogl B, Heidbreder A, Santamaria J, Graus F, Poewe W. IgLON5 autoimmunity and abnormal behaviours during sleep. Lancet 2015;385:1590.

15.   Montojo T, Piren V, Benkhadra F, Codreanu A, Diederich NJ. Gaze Palsy, Sleep and Gait Disorder, as Well as Tako-Tsubo Syndrome in a Patient with IgLON5 Antibodies. Movement disorders clinical practice 2017;4:441-443.

16.   González-Ávila C, Casado L, Muro García I, Villacieros-Álvarez J, Vivancos J, Quintas S. Altered ioflupane single-photon emission computed tomography in anti-IgLON5 disease: A new case mimicking probable progressive supranuclear palsy and review of the literature. European journal of neurology 2021;28:1392-1395.

17.   Montagna M, Amir R, De Volder I, Lammens M, Huyskens J, Willekens B. IgLON5-Associated Encephalitis With Atypical Brain Magnetic Resonance Imaging and Cerebrospinal Fluid Changes. Front Neurol 2018;9:329.

18. Moreno-Estebanez A, Garcia-Ormaechea M, Tijero B, Fernandez-Valle T, Gomez-Esteban JC, Berganzo K. Anti-IgLON5 Disease Responsive to Immunotherapy: A Case Report with an Abnormal MRI. Movement disorders clinical practice 2018;5:653-656.

19. Nissen MS, Blaabjerg M. Anti-IgLON5 Disease: A Case With 11-Year Clinical Course and Review of the Literature. Front Neurol 2019;10:1056.

20. Villacieros-Álvarez J, Ordás CM, Torres-Gaona G, Díez-Barrio A, Prieto-Jurczynska C, Gaig C. Anti-IgLON5 Disease: A Long-course Presentation with a Response to Immunotherapy. Neurology 2020. doi: 10.1212/WNL.0000000000011381.

21. Chung HY, Wickel J, Voss A, et al. Autoimmune encephalitis with anti-IgLON5 and anti-GABAB-receptor antibodies: A case report. Medicine (Baltimore) 2019;98:e15706.

22. Asioli GM, Calandra-Buonaura G, Mastrangelo V, et al. Persistence of Facio-Skeletal Myorhythmia During Sleep in anti-IgLON5 Disease. Movement disorders clinical practice 2021;8:460-463.

23. Honorat JA, Komorowski L, Josephs KA, et al. IgLON5 antibody: Neurological accompaniments and outcomes in 20 patients. Neurol Neuroimmunol Neuroinflamm 2017;4:e385.

24. Wenninger S. Expanding the Clinical Spectrum of IgLON5-Syndrome. Journal of neuromuscular diseases 2017;4:337-339.

25. Schoberl F, Levin J, Remi J, et al. IgLON5: A case with predominant cerebellar tau deposits and leptomeningeal inflammation. Neurology 2018;91:180-182.

26. Fahn S. Classification of movement disorders. Mov Disord 2011;26:947-957.

27.   Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129-2170.

28.   Hoglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord 2017;32:853-864.

29.   Boxer AL, Yu JT, Golbe LI, Litvan I, Lang AE, Hoglinger GU. Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches. Lancet Neurol 2017;16:552-563.

30.   Respondek G, Stamelou M, Kurz C, et al. The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases. Mov Disord 2014;29:1758-1766.

31.   Raccagni C, Nonnekes J, Bloem BR, et al. Gait and postural disorders in parkinsonism: a clinical approach. J Neurol 2020;267:3169-3176.

32.   Nonnekes J, Goselink RJM, Růžička E, Fasano A, Nutt JG, Bloem BR. Neurological disorders of gait, balance and posture: a sign-based approach. Nat Rev Neurol 2018;14:183-189.

33.   Fanciulli A, Wenning GK. Multiple-system atrophy. N Engl J Med 2015;372:249-263.

34.   Cardoso F. Autoimmune choreas. J Neurol Neurosurg Psychiatry 2017;88:412-417.

35.   Vigliani MC, Honnorat J, Antoine JC, et al. Chorea and related movement disorders of paraneoplastic origin: the PNS EuroNetwork experience. J Neurol 2011;258:2058-2068.

36.   O'Toole O, Lennon VA, Ahlskog JE, et al. Autoimmune chorea in adults. Neurology 2013;80:1133-1144.

37.   Aylward EH, Sparks BF, Field KM, et al. Onset and rate of striatal atrophy in preclinical Huntington disease. Neurology 2004;63:66-72.

38.   Aslam S, Shill H. Chorea in IgLON5-Mediated Autoimmune Encephalitis. Movement disorders clinical practice 2020;7:S83-s84.

39.   Haitao R, Yingmai Y, Yan H, et al. Chorea and parkinsonism associated with autoantibodies to IgLON5 and responsive to immunotherapy. J Neuroimmunol 2016;300:9-10.

40.   Varley JA, Webb AJS, Balint B, et al. The Movement disorder associated with NMDAR antibody-encephalitis is complex and characteristic: an expert video-rating study. J Neurol Neurosurg Psychiatry 2019;90:724-726.

41.   Pittock SJ, Parisi JE, McKeon A, et al. Paraneoplastic jaw dystonia and laryngospasm with antineuronal nuclear autoantibody type 2 (anti-Ri). Arch Neurol 2010;67:1109-1115.

42.   Doppler K, Schleyer B, Geis C, et al. Lockjaw in stiff-person syndrome with autoantibodies against glycine receptors. Neurol Neuroimmunol Neuroinflamm 2016;3:e186.

43.   Baizabal-Carvallo JF, Cardoso F, Jankovic J. Myorhythmia: phenomenology, etiology, and treatment. Mov Disord 2015;30:171-179.

44.   Simpson DA, Wishnow R, Gargulinski RB, Pawlak AM. Oculofacial-skeletal myorhythmia in central nervous system Whipple's disease: additional case and review of the literature. Mov Disord 1995;10:195-200.

45.   Vetter E, Olmes DG, Linker R, Seifert F. Teaching Video NeuroImages: Facial myokymia and myorhythmia in anti-IgLON5 disease: The bitten lip. Neurology 2018;91:e1659.

46.   Baizabal-Carvallo JF, Stocco A, Muscal E, Jankovic J. The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. Mov Disord 2013;28:543-547.

47.   Fuseya K, Kimura A, Yoshikura N, Yamada M, Hayashi Y, Shimohata T. Corticobasal Syndrome in a Patient with Anti-IgLON5 Antibodies. Movement disorders clinical practice 2020;7:557-559.

48.   Logmin K, Moldovan AS, Elben S, Schnitzler A, Groiss SJ. Intravenous immunoglobulins as first-line therapy for IgLON5 encephalopathy. J Neurol 2019;266:1031-1033.

49.   Brunetti V, Della Marca G, Spagni G, Iorio R. Immunotherapy improves sleep and cognitive impairment in anti-IgLON5 encephalopathy. Neurol Neuroimmunol Neuroinflamm 2019;6:e577.

50.   Escudero D, Guasp M, Arino H, et al. Antibody-associated CNS syndromes without signs of inflammation in the elderly. Neurology 2017;89:1471-1475.

Legend of videos

Video 1 Gait instability with impaired balance. Unsteady gait with altered postural reflexes in a 71 year-old woman with a PSP-like phenotype.

Video 2 Cerebellar gait ataxia. A wide based gait with irregular stepping and ataxic voice in a 61 year-old woman with 4 years history of gait difficulties.

Video 3 Chorea. Generalized choreic movements involving the four limbs and trunk is shown in 2 patients.

Video 4 Chorea with isolated orofacial involvement. In a 46 year-old man with a bulbar phenotype that required tracheostomy for episodes of respiratory failure. He also rocks back and forth secondary to akathisia.

Video 5 Parkinsonism. A 61 year-old man with parkinsonism, slow and shuffling gait, and abnormal posture with a Pisa syndrome. A 58 year-old female with asymmetric parkinsonism of subacute onset with reduced right arm swing on gait.

Video 6 Dystonia. A 74 year-old man presented with continuous dystonic movements involving the tongue and also the abdomen, thorax and shoulders. Abnormal body postures with antecollis and antero-lateral bending of the trunk is also shown

Video 7 Lingual myorhythmia. A 62 year-old man consulted because of these rhythmic slow movements affecting the tongue.

Video 8 Facial myokymia. A 69 year-old woman with cognitive impairment, chorea and sleep problems. Facial myokymia, mainly involving the lower face muscles, is also present.

Table 1. Demographic data and clinical features of 72 patients with IgLON5 antibodies

Variable	N (%)
Age at disease onset	62 (42-91)[a]
Gender, male	40 (56)
Chronic presentation (in >4 months)	55 (76)
Age at diagnosis	66 (46-91)[a]
Time (months) from onset to diagnosis	36 (1-216)[a]
Concomitant autoimmune diseases [b]	6 (8%)
History of cancer [c]	7 (10%)
Main complaints leading to consultation [d]	
Gait problems	29 (40)
Sleep disturbances	23 (32)
Movement disorders [e]	19 (26)
Bulbar symptoms	17 (24)
Cognitive problems	13 (18)
Other [f]	7 (10)
Clinical phenotypes at diagnosis	
Movement disorders [g]	27 (37)
Bulbar syndrome	17 (24)
Cognitive disorder	12 (17)
Sleep disorder	11 (15)
Neuromuscular [h]	5 (7)
Brain MRI [i]	
Normal or non-specific changes	58/70 (83)
Brainstem atrophy	6/70 (9)
Cerebellar atrophy	3/70 (4)
Other abnormalities	3/70 (4)
CSF analysis [j]	
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)

[a] Median and range.

[b] Factor VIII deficiency (1), erythema nodosum (1), polymyalgia rheumatica (1), thyroiditis (1), diabetes mellitus type 1 (1), hypothyroidism (1).

[c] Breast cancer (2), thyroid cancer (1), kidney carcinoma (1), gastrointestinal neuroendocrine tumour (1), adrenal adenoma and pulmonary nodules (1), bladder carcinoma (1).

[d] 28 patients had >1 presenting symptom: 2 symptoms (20), 3 symptoms (8).

[e] Chorea (9), facial/abdominal dyskinesias (6), rigidity/spasms (2), parkinsonism (2).

[f] Fasciculations and weakness (3), oculomotor symptoms (3), neuropathic pain (1).

[g] Gait impairment with oculomotor abnormalities resembling progressive supranuclear palsy (10), facial/abdominal dyskinesias (7), cerebellar ataxia (4), chorea (4), parkinsonism (1), limb rigidity and spasms (1).

[h] Motor neuron-like disease (4), painful polyneuropathy (1).

[i] Brain MRI could not be performed in 2 patients. Other abnormalities included encephalitic-like hyperintensities (1), hippocampal atrophy (1) and putaminal hyperintensity (1).

[j] 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).

Table 2. Movement disorders in 72 patients with anti-IgLON5 disease

Abnormal movement	N (%)	Associated features	N (%)
Gait disorder	**52 (72)**	**Type of gait disorder [b]**	
Reason for consultation	29 (40)	Disequilibrium	20/52 (38)
Major symptom [a]	31 (43)	Cerebellar ataxia	17/52 (33)
		Disequilibrium/ataxia	9/52 (17)
		Parkinsonian	4/52 (8)
		Choreic	2/52 (4)
Chorea	**24 (33)**	**Topography**	
Reason for consultation	9 (12)	Limb	20/24 (83)
Major symptom	12 (17)	Facial	18/24 (75)
		Axial (trunk, neck)	11/24 (46)
Bradykinesia	**20 (28)**	**Associated features:**	
Reason for consultation	2 (3)	Rigidity	10/20 (50)
Major symptom	4 (6)	Rest tremor	2/20 (10)
		Gaze palsy	15/20 (75)
Dystonia	**19 (26)**	**Topography [d]**	
Reason for consultation	3 (4) [c]	Cranial	15/19 (79)
Major symptom	7 (10)	Limb	7/19 (37)
		Trunk (abdomen)	1/19 (5)
Abnormal body postures and rigidity	**18 (25)**	**Topography**	
		Antecollis	8/18 (44)
Reason for consultation	2 (3) [e]	Trunk bended or flexed	6/18 (33)
Major symptom	5 (7)	Limb Rigidity/Stiffness	5/18 (28)
Tremor	**15 (21)**	**Type**	
Reason for consultation	1 (1) [f]	Action upper limb tremor	13/15 (87)
Major symptom	1 (1)	Rest tremor	2/15 (13)
		Cephalic tremor	2/15 (13)
		Voice tremor	1/15 (7)
Other hyperkinesias	**26 (36)**	**Type**	

Reason for consultation	3 (4) [g]	Myoclonus	9/26 (35)
Major symptom	10 (14)	Akathisia	9/26 (35)
		Myorhythmia	6/26 (23)
		Myokymia	4/26 (15)
		Abdominal dyskinesia	2/26 (8)

[a] Major symptom was defined as a prominent manifestation at the time of anti-IgLON5 diagnosis, as stated by the treating neurologist.

[b] Most patients presented a gait disorder that combined postural instability with other features (see text).

[c] Mandibular dystonia in 2 patients and trunk dystonia in 1.

[d] 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)

[e] Muscle stiffness with spasms in 2.

[f] One patient consulted because rest tremor associated with motor slowness.

[g] Myorhythmia in 2 patients and abdominal dyskinesias in 1.

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)
NREM parasomnia in v-PSG	26/38 (68)
REM sleep behavior disorder in v-PSG [a]	19/31 (61)
Insomnia (sleep onset and/or fragmentation)	39 (54)
Excessive daytime sleepiness	37 (51)
Bulbar dysfunction	**53 (74)**
Dysphagia [b]	42 (58)
Dysarthria	38 (53)
Episodes of acute respiratory failure [c]	18 (25)
Stridor during wakefulness	11 (15)
Vocal cord palsy on laryngoscopy	17/29 (59)
Oculomotor abnormalities	**45 (62)**
Gaze palsies [d]	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)

[a] Confirmed by video-polysomnography (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 up-ward and down-ward: 9). Horizontal gaze palsy in 13 (to both sides in 10). Nine patients had both, vertical and horizontal gaze palsy. Only 2 patients (one with a cognitive subtype, and another with a motor neuron like syndrome) had vertical gaze palsy with predominant downgaze involvement.

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*
Age at disease onset	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 (months)	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

Data are reported as median and range, or number and percentage.

Legend of figures

Figure 1: Frequency of the different clinical phenotypes in 72 patients with anti-IgLON5 disease
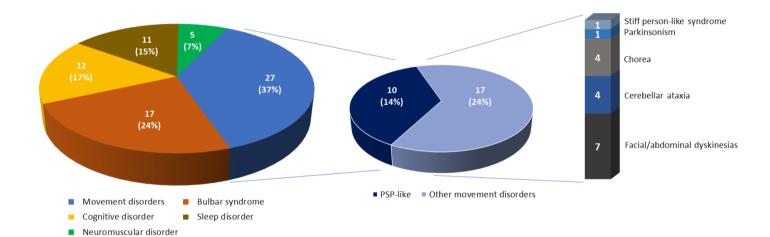
PSP: Progressive supranuclear palsy.

Figure 2: Relation between the movement disorder type and main anti-IgLON5 disease manifestations

Frequency of the nine most common movement disorders (in blue) in each anti-IgLON5 disease phenotype (in gray). Patients with PSP-like manifestations are shown separate from the remaining patients with movement disorders phenotype. PSP: progressive supranuclear palsy. Movement Dis: Movement disorders.

Figure 3: Interactions between different movement disorders in anti-IgLON5 disease

In this chord diagram, each movement disorder is represented by a fragment of the circular layout and arcs represent the number of interactions between different movement disorders. Ab.body.post/rigid.: Abnormal body postures and rigidity; Myorh/Myok: Myorhythmia and myokymia; Akhat.; Akathisia

Left pie chart:

- 27 (37%) — Movement disorders
- 17 (24%) — Bulbar syndrome
- 12 (17%) — Cognitive disorder
- 11 (15%) — Sleep disorder
- 5 (7%) — Neuromuscular disorder

Legend:
■ Movement disorders ■ Bulbar syndrome
■ Cognitive disorder ■ Sleep disorder
■ Neuromuscular disorder

Right pie chart:

- 10 (14%) — PSP-like
- 17 (24%) — Other movement disorders

Legend:
■ PSP-like ■ Other movement disorders

Bar breakdown:

- 1 — Stiff person-like syndrome
- 1 — Parkinsonism
- 4 — Chorea
- 4 — Cerebellar ataxia
- 7 — Facial/abdominal dyskinesias

Movement disorder: n (%)
Clinical phenotype (n)

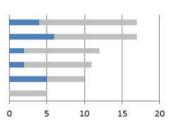**Gait disorder: 52 (72)**

Bulbar (n=17)
Movement Dis (n=17)
Cognitive (n=12)
Sleep (n=11)
PSP-like (n=10)
Neuromuscular (n=5)

0   5   10   15   20

Chorea: 24 (33)

0   5   10   15   20

Bradykinesia: 20 (28)

0   5   10   15   20

Movement disorder: n (%)
Clinical phenotype (n)

Dystonia: 19 (26)

Bulbar (n=19)
Movement Dis (n=17)
Cognitive (n=12)
Sleep (n=11)
PSP-like (n=10)
Neuromuscular (n=5)

0   5   10   15   20

Tremor: 15 (21)

0   5   10   15   20

Abnormal body postures and rigidity: 18 (25)

0   5   10   15   20

Movement disorder: n (%)
Clinical phenotype (n)

Myorhythmia/Myokymia: 10 (14)

Bulbar (n=17)
Movement Dis (n=17)
Cognitive (n=12)
Sleep (n=11)
PSP-like (n=10)
Neuromuscular (n=5)

0   5   10   15   20

Akathisia: 9 (12)

0   5   10   15   20

Myoclonus: 9 (12)

0   5   10   15   20