Abstract

Objective: To develop a composite score to assess the severity of the multiple symptoms present in anti-IgLON5 disease.

Methods: The anti-IgLON5 disease composite score (ICS) was designed to evaluate 17 symptoms divided in 5 clinical domains (bulbar, sleep, movement disorders, cognition, others). Each symptom was scored from 0 (absent/normal) to 3 or 6 (severe) depending on the contribution of the symptom to neurologic disability with a maximum ICS of 69. The ICS was tested in patients from two cohorts (Barcelona, Spain, and GENERATE, Germany) that included cases personally seen by the authors (internal) and patients whose ICS was obtained from information of questionnaires completed by the referring neurologists (external). Test-retest and inter-rater reliability of the ICS was assessed by the intraclass coefficient (ICC) and the correlation between the ICS and the modified Rankin scale (mRS) with the non-parametric Spearman's rank coefficient. The Wilcoxon signed-ranks test was used to compare the ICS at diagnosis of anti-IgLON5 disease and follow-up in a subset of patients with available clinical information.

Results: A total of 86 patients (46 from Barcelona cohort; 40 from GENERATE cohort) were included. The median ICS was 15 (range: 2-31). The ICS was higher in the Barcelona than in the German cohort (18 vs 12, $p<0.001$), due to higher partial scores in sleep and movement disorder domains. There were no significant differences in the ICS between internal and external patients (15 vs 14, $p= 0.96$). The ICS correlated with the mRS score ($r = 0.429$, $p <0.001$). Test-retest and inter-rater reliability were excellent with an ICC of 0.997 (95% CI: 0.992-0.999) and 0.973 (95% CI: 0.925-0.990) respectively. ICS was re-tested during follow-up in 27 patients and it was similar to that at diagnosis in 10 clinically stable patients (median ICS at diagnosis: 11.5 versus 11.5 at

follow-up; p= 1), higher in 8 patients who worsened (12.5 vs 18; p= 0.012), and lower in 9 patients who improved after immunotherapy (14 vs 10; p= 0.007).

Discussion: The ICS is a valid method to assess the extension and severity of the different clinical manifestations of anti-IgLON5 disease.

Introduction

Anti-IgLON5 disease is a clinically heterogeneous neurological disorder that can present with a broad spectrum of clinical manifestations.[1] Disease development is slowly progressive in about two thirds of the patients and subacute in the rest.[2] Progressive clinical manifestations include a combination of bulbar symptoms, mainly dysarthria, dysphagia, and vocal cord paralysis, gait instability, and abnormal movements being the most common generalized chorea and facial dyskinesias.[3] Sleep is frequently abnormal showing non-rapid eye movements (NREM) and REM sleep parasomnias, stridor, and obstructive sleep apnea.[4] According to the predominating symptoms, 5 clinical phenotypes have been reported: 1) sleep disorder; 2) bulbar syndrome; 3) movement disorders, including a syndrome resembling progressive supranuclear palsy; 4) cognitive impairment; and 5) neuromuscular manifestations with muscle weakness, atrophy, or fasciculations.[3, 5-7]

The hallmark of the disease is the presence of antibodies against IgLON5, a cell adhesion molecule preferentially expressed in neurons.[1] Even though initial studies showed neuronal deposits of phosphorylated tau protein predominantly involving the tegmentum of the brainstem, a primary autoimmune pathogenesis is supported by 1) the robust association with the human leukocyte antigen (HLA) haplotype DRB1*10:01- DQB1*05:01detected in 60% of patients, 2) autopsy studies showing absence of neuronal deposits of phosphorylated tau in some patients with IgLON5 antibodies, 3) antibody studies demonstrating that they cause irreversible internalization of IgLON5 and induce cytoskeletal alterations in cultured rat hippocampal neurons, and 4) presence of CSF inflammatory changes and at least partial response to immunotherapy in patients investigated in early stages of the disease.[1, 2, 8-10]

The severity of anti-IgLON5 disease and the effect of the immunotherapy are currently assessed with the modified Rankin scale (mRS) which measures the impact of neurological symptoms in the activities of daily living (ADL).[2, 3, 10] However, considering

the diversity of symptoms and the increasing interest in the use of immunotherapies, we reasoned that the assessment of symptom severity with mRS is inadequate for this disease and that a better instrument is required to 1) assess the severity of the different symptoms of anti-IgLON5 disease, 2) monitor its evolution during the clinical course, and 3) provide an objective measure of the effects of immunotherapy. With these aims in mind, we first developed a composite score that rates the most common symptoms of anti-IgLON5 disease, and we then applied the score to two cohorts of patients.

Methods

Definition and development of the anti-IgLON5 disease composite score (ICS)

A first version of the ICS was developed in English by three investigators (CG, FG, JS) and later independently tested in 20 patients (10 in Barcelona, Spain, and 10 in Bochum, Germany) to look for potential pitfalls. After this first evaluation, the ICS was reviewed by all the authors in several telematic meetings and modified until a consensus was achieved. The ICS was completed prospectively by the treating physician along with the patient and caregiver, or retrospectively through a questionnaire provided to the referring physician, as reported.[2-4] The ICS has 5 domains that cover the main clinical manifestations of anti-IgLON5 disease, including 17 symptoms: 1. bulbar (4 symptoms), 2. sleep (4), 3. movement disorders (4), 4. cognition (2), and 5. other symptoms (3, oculomotor abnormalities, dysautonomia, and neuromuscular symptoms – mainly fasciculations-) (Table 1).

Each clinical domain provides a partial ICS score obtained from the quantitative assessment of the corresponding symptoms, resulting in a total ICS score of 69. Each individual symptom was rated as: absent/normal (score = 0); mild, the symptom does not interfere with ADL (score = 1); moderate, the symptom interferes with some ADL

or has an impact in patient's quality of life (score = 2), and severe, the symptom has a substantial impact in ADL (score = 3). The score was rated 6, instead of 3, when stridor, central hypoventilation, dysphagia, gait difficulties, cognitive impairment, or neuropsychiatric manifestations, were considered severe. This higher score serves to weigh better the more severe disability caused by the indicated symptoms. If a symptom could not be evaluated, it was recorded as missing and scored 0. Definitions of mild, moderate, and severe for each symptom are provided in Table 2. Most symptoms can be graded by plain clinical assessment without the need of paraclinical studies. An exception is the assessment of nocturnal stridor, obstructive sleep apnea and abnormal movements and behaviors during sleep, which ideally should be graded after a video-polysomnogram or a home video recording instead of information provided by the bed partner. Similarly, the degree of cognitive impairment should be based on cognitive scales (for example the Montreal Cognitive Assessment (MoCA) scale).

Patients

The ICS was tested in patients with anti-IgLON5 disease from two different cohorts recruited at Hospital Clinic de Barcelona (Barcelona, Spain), and the GENERATE (GErman NEtwork for REsearch on AuToimmune Encephalitis) registry summarized for this study in the St. Josef Hospital, University Hospital of the Ruhr-University Bochum. Both cohorts include patients diagnosed and followed at the indicated centers as well as patients from other centers of Spain, Germany, and other countries whose information was provided to the two reference hospitals. Clinical information at diagnosis of anti-IgLON5 disease was collected prospectively in both centers using structured questionnaires completed by the treating neurologist, as reported.[2-4] The questionnaire included information regarding the presence and severity of anti-IgLON5 symptoms and mRS score.

Cohort testing

The final version of ICS was applied to patients consecutively identified with anti-IgLON5 disease based on clinical information obtained by the time IgLON5 antibodies were detected. Patients with more than 3 missing symptoms were excluded. Demographic and clinical data were compared between patients from Hospital Clinic and GENERATE to identify major differences before the application of the ICS. The ICS, partial scores for each domain, and individual symptom scores were analyzed taking in consideration whether the information had been directly obtained from investigators at the 2 reference centers (internal patients), or through questionnaires sent to physicians of outside facilities (external patients). The ICS and partial scores were also compared with the mRS score and analyzed according to the clinical phenotype that was defined by the predominant symptoms by the time IgLON5 antibodies were detected, as reported.[3] To assess whether the ICS was able to detect clinical changes over the course of the disease, the ICS was rescored in a subset of patients with reliable clinical follow-up information.

Statistical analysis

Statistical analysis was performed using SPSS 25.0 for Windows (SPSS, Inc., Chicago, IL). The ICS, partial scores for each domain, and individual symptom's score were reported as median and range, or number and percentage. Data were tested for normal distribution using the Kolmogorov-Smirnov test. For group comparisons, Chi-square and Fisher exact probability test were used for qualitative variables and the non-parametric Mann Whitney's U test for quantitative variables. *P* values less than 0.05 were considered significant.

For ICS partial scores, ceiling effect was present if >15% of patients achieved the maximal score. Proportion of patients with a partial score of 0 was also calculated for each domain. Frequency distribution of the scoring of each individual symptom was also evaluated to assess the presence of infrequent scores (<5%). Correlations between the ICS and the mRS, age at diagnosis (or detection of IgLON5 antibodies) and diagnostic delay (time from symptoms onset to detection of IgLON5 antibodies, when the ICS was applied) were assessed with non-parametric Spearman's rank coefficient.

Cronbach's alpha coefficient was used to measure items dependencies and intercorrelations. Evaluation of inter-rater reliability and test-retest stability was done in 20 patients. In each center two neurologists independently calculated a score for 10 randomly selected patients. To assess test-retest stability the scale was re-calculated 1 month later by the same 2 neurologists at each center. Inter-rater and test-retest reliability was measured by the Cohen's kappa coefficient for each individual symptom's score and by intraclass coefficient (ICC) for ICS total and partial scores. The Wilcoxon signed-ranks test was used to compare differences in the ICS obtained at diagnosis of anti-IgLON5 disease and during follow-up visits.

Standard protocol approvals, registrations, and patient consents

The Ethic Committees of the Hospital Clinic Barcelona (Reg. no HCB/2021/0223) and of the University Lübeck (vote-no. 13-162) approved the study. All patients or proxies gave written informed consent for use of clinical information for research purposes.

Data availability

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

Results

Study population and application of ICS

The 86 patients included in the study (46 from Hospital Clinic de Barcelona, 40 from GENERATE) represented 79% and 74% of all patients with anti-IgLON5 disease registered until October 1st, 2022 in Hospital Clinic and GENERATE respectively; from the remaining cases (21% and 26%) the clinical information was incomplete as the presence or severity of more than 3 symptoms was unknown. Demographic and clinical features of the 86 patients are shown in Table 3. Forty-seven (55%) patients were male with a median age of 66 years (range: 46-91 years) at the time of IgLON5 antibodies detection. Demographic and clinical variables were similar in both cohorts (Barcelona, GENERATE) except for an overrepresentation of patients with a cognitive phenotype in the Barcelona cohort (Table 3). Demographic and clinical features were also similar in patients seen by the investigators (internal patients) and those whose information was provided by referring physicians (external patients) (eTable 1). Therefore, we did not identify major differences that prevented the merging of both cohorts in order to analyze the ICS.

The total ICS and domain partial scores are shown in Table 4. The median total ICS was 15 (range: 2-31) (Figure 1.A). The ICS was significantly higher in patients from the Barcelona cohort than in those from the GENERATE cohort (median ICS: 18 vs 12, $p<0.001$, Figure 1.B and 1.C). Partial scores for movement disorders and sleep domains were higher in the Barcelona cohort compared with the GENERATE cohort, whereas the scores of the remaining domains were similar in both cohorts (Table 4). Partial scores for each domain of the 86 patients are presented in Figure 1D. There were no significant differences in the global ICS and partial scores comparing internal and

external patients with the exception that sleep symptoms rated higher in internal patients (median score: 5.5 vs. 3.0; p = 0.03, Table 4).

The ICS increased with disease severity and showed a good correlation with the mRS score (r = 0.429, p <0.0001, Figure 2.A). Median ICS was 13 in patients with mRS 1-2, 14 in patients with mRS 3, and 19 in patients with mRS 4-5 (p=0.001). The correlation with mRS was weaker when all the items defined as severe were scored as 3, without any weighting (r = 0.281, p =0.009). The mRS also correlated with partial scores for bulbar symptoms (r = 0.216, p=0.045), movement disorders (r = 0.339, p=0.001) and cognition (r = 0.345, p=0.001), but not with partial scores for sleep (r= -0.027, p=0.80) and other symptoms' partial score (r = -0.001, p=0.99). Regarding clinical phenotypes, the ICS value was similar except for patients with neuromuscular phenotype that had a lower ICS (Figure 2.B). Partial scores of the 5 domains according to clinical phenotypes are shown in Table 5. As expected, the highest partial scores in each domain were recorded in patients with the corresponding clinical phenotype (eg, sleep clinical phenotype has the highest partial score in the sleep domain). Only 3 (3.5%) of the 86 patients had one system involved (cognitive, bulbar, or movement disorders) whereas 83 (96.5%) scored positive in several partial domains: 9 patients scored in 2 domains, 11 patients in 3, 35 patients in 4, and 28 in all five domains. The ICS did not correlate with the diagnostic delay (r = 0.105, p=0.33) or patient's age by the time IgLON5 antibodies were detected (r = 0.116, p=0.29).

The ICS was rescored in 27 patients (15 from Hospital Clinic of Barcelona, 12 from GENERATE) during follow-up. Ten patients were clinically stable after a median follow-up of 13.5 months (range 12-17) and their follow-up ICS (median: 11.5) was unchanged compared to that obtained at diagnosis of anti-IgLON5 disease (11.5; mean rank 1.5, z=0.0, p=1). Eight patients had worsening of their symptoms after a median

follow-up of 25 months (range: 6-52) and their median ICS increased from 12.5 to 18 (mean rank 4.5, z= -2.5, p=0.012). By contrast, 9 patients who improved with immunotherapy after a median follow-up of 10 months (range 3-38), showed a median ICS that was significantly reduced compared to that obtained at diagnosis of the disease (10 versus 14; mean rank 5, z= -2.7, p=0.007).

Missing data, score distribution of each symptom and ICS reliability

Thirty (35%) of the 86 patients had at least one missing item (one in 4 patients; two in 5; and three in 21). The percentage of missing items was low for almost all symptoms (ranging from 0 to 3%) except for stridor (24%), obstructive sleep apnea (25%) and insomnia (30%), that accounted for 90% of missing items (eTable 2). The proportion of patients with missing data was significantly higher in the GENERATE cohort than in the Barcelona cohort (25/40 (62.5%) vs 5/46 (10.9%), p<0.001), and in the external patients compared with the internal cases (28/58 (48.3%) vs 2/28 (7.1%), p<0.001) (eTable 3).

The ICS had a normal distribution (Kolmogorov-Smirnov test p=0.2, ICS mean 14.5 ± standard deviation 6.5, interquartile range 9). Ceiling effect was absent as only 2 (2.3%) patients reached the maximal partial score in a domain (both for cognition). Minimal partial score of 0 was seen in 13 (15%) patients for bulbar symptoms, 10 (12%) for sleep symptoms, 18 (21%) for movements disorders, 36 (42%) for cognition, and 20 (23%) for other symptoms (Figure 1.D). Regarding the scoring distribution of individual symptoms, all score options (absent, mild, moderate, or severe) were obtained at least once for all 17 symptoms. Only 6 (8.8%) out of the 68 possible scores (4 x 17 symptoms) were infrequently assigned. They included: mild central

hypoventilation, severe chorea, severe orofacial dyskinesias, severe other movement disorder, moderate dysautonomia and severe fasciculations (eTable 2).

Cronbach's alpha for the ICS was 0.308, indicating a low level of redundancy between items of the scale. When each symptom domain was assessed separately, the Cronbach's alpha coefficient increased only for bulbar, sleep, and cognition domains (eTable 4), but without reaching a value higher than 0.7, which is the threshold indicative of item dependency or redundancy. Test-retest (or intra-rater) reliability was very high for total ICS and partial scores of the five domains with an ICC > 0.980 in all instances (eTable 5). Inter-rater reliability was also excellent (ICC > 0.900 in the ICS and all its domains, eTable 5). Similarly, test-retest reliability was very high for all symptoms (Cohen's kappa coefficient > 0.81) except for neuropsychiatric symptoms which had a coefficient of 0.79 (eTable 6). Inter-rater reliability for individual symptom's score was less optimal, with an agreement ranging from moderate to substantial in most items (eTable 6).

Discussion

We developed the ICS in order to provide an objective measure of the presence and severity of anti-IgLON5-associated symptoms and to monitor the response to immunotherapy and progression of the disease. The ICS showed a good correlation with the mRS and was able to capture clinical stability or changes (either symptom worsening or improvement) over the course of the disease, indicating that it can be used for the evaluation of the effects of immunotherapy and how treatment impacts on each individual symptom of the disease, an assessment that the mRS is unable to provide.

The ICS did not correlate with the delay in the diagnosis. This finding is expected as the clinical course of anti-IgLON5 disease is variable. Up to 30% of patients have a subacute progression of symptoms reaching the maximal clinical

severity in a few months. [2,10] In contrast, the other 70% of patients have a more protracted course, showing long periods of symptom stabilization followed by sudden deterioration that can be caused by the development or worsening of a distinct symptom (i.e. gait instability, dysphagia).[5, 6] A task for the future is to assess better the ability of ICS in detecting and quantifying new or worsening symptoms that contribute to clinical deterioration, including those not captured by the mRS.

The total ICS was significantly higher in the Barcelona cohort than in the GENERATE cohort. This likely reflects the larger number of missing items in the sleep domain in the GENERATE cohort and the higher partial score in the movement disorders domain in the Barcelona cohort which was comprehensively assessed for a recent report.[3] Moreover, since Hospital Clinic has a center for Sleep Disorders with investigations focused on anti-IgLON5 disease, sleep symptoms have been assessed in more detail, explaining the low rate of missing data and the higher partial score for the sleep domain compared with the GENERATE cohort.[7, 8]

The ICS provides partial scores for five clinical domains that encompass most, if not all, symptoms observed in anti-IgLON5 disease. Analysis of the partial scores for each domain supports the clinical phenotypes previously described in anti-IgLON5 disease;[3, 10] accordingly, the highest partial score for each domain occurred in the group of patients with the corresponding clinical phenotype. The good correlation between the mRS and ICS partial scores of bulbar, movement disorders, and cognitive domains but not sleep and other symptoms domains are explained by the higher impact of respiratory difficulties, gait impairment, and cognitive status, in the mRS. In contrast, sleep problems and other symptoms, such as oculomotor abnormalities or fasciculations, have a lower impact on the mRS.

The ICS is easy to apply and mostly depends on the clinical interview and examination of the patient. An interview with the patient's caregiver is crucial for the evaluation of some symptoms, and video-polysomnography data is particularly important to score the symptoms associated with sleep. The ICS can also be calculated based on the structured questionnaires completed by referring physicians as the total and partial scores did not differ between internal and external patients. The only exception was the severity of sleep symptoms that was assessed as higher in internal patients. This limitation should be solved in future prospective studies in which the ICS will we obtained by the treating physician and the video-polysomnography will become a standard test in the evaluation of anti-IgLON5 disease.

Test-retest and interrater agreement of ICS was high. The reliability was rated excellent for the total score and partial scores. It is likely that the definitions provided to rate the severity of symptoms helped to achieve the high agreement observed in the test-retest and interrater assessment. Unlike in other scales that evaluate an uniform syndrome (i.e.: cerebellar ataxia),[16] internal consistency was not an issue of the ICS that evaluates very different clinical manifestations.[17]Items of the ICS were independent and not redundant, and consequently, valid to measure the heterogeneous symptoms of the indicated clinical phenotypes of anti-IgLON5 disease. The ICS was also able to reflect symptom stability, improvement after immunotherapy, or worsening caused by disease progression or relapses. Although this ability to detect clinical changes was evaluated retrospectively in a small subset of patients, our findings suggest that the ICS could be used as a tool in future prospective longitudinal studies assessing the natural course of the disease and response to immunotherapies.

The main limitation of this study is that ICS was tested retrospectively in a substantial number of patients using information provided by questionnaires and

rescoring was assessed in a small number of patients. The novelty and low frequency of anti-IgLON5 disease poses important difficulties to prospectively develop and validate a scale using consecutively diagnosed patients, even using multicenter efforts. However, when the ICS of internal patients was compared with that of external cases (obtained from questionnaires), the values were similar, suggesting that there were no significant biases derived from the inclusion of patients that were retrospectively assessed. Another potential limitation is that the ICS may not be useful in very rare instances in which patients present with atypical symptoms not well reflected in the ICS as for example seizures.[18]

Overall, the findings of this study suggest that ICS is a valid instrument to capture the extension and severity of the different clinical manifestations of anti-IgLON5 disease. Future prospective studies should assess the ability of ICS to measure the effect of immunotherapy in these patients and to demonstrate changes related to the course of the disease.

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Table 1. Anti-IgLON5 disease composite score (ICS)

Domain	Points*
Bulbar	Partial Score: 0-21
Stridor	0-1-2-6
Central hypoventilation	0-1-2-6
Dysphagia	0-1-2-6
Dysarthria	0-1-2-3
Sleep	Partial score: 0-12
Abnormal movements/behaviors-vocalizations	0-1-2-3
Insomnia	0-1-2-3
Excessive daytime sleepiness	0-1-2-3
Obstructive sleep apnea	0-1-2-3
Movement disorders	Partial score: 0-15
Gait difficulties and falls	0-1-2-6
Chorea	0-1-2-3
Orofacial dyskinesias	0-1-2-3
Other movement disorders. Specify:	0-1-2-3
Cognition	Partial score: 0-12
Cognitive impairment	0-1-2-6
Neuropsychiatric (psychosis, delirium)	0-1-2-6
Other	Partial score: 0-9
Oculomotor abnormalities	0-1-2-3
Dysautonomia	0-1-2-3
Fasciculations	0-1-2-3
Total composite score	0-69

*0: Absent / normal; 1: Mild; 2: Moderate; 3 (or 6): Severe. Guidelines for the definition of mild, moderate, and severe for each item are included in Table 2.

Table 2. Guidelines for the definition of mild, moderate, and severe scores

Score (points)	Mild (1)	Moderate (2)	Severe (3 or 6)
Symptom			
Stridor [1]	Occasional stridor during sleep	Frequent stridor during sleep, controlled with CPAP	Continuous stridor during sleep not controlled with CPAP, stridor during wakefulness or tracheostomy needed for stridor
Central hypoventilation	Only detected in nocturnal video-PSG but no need of ventilation	Non-invasive nocturnal ventilation required	Needs ICU admission or mechanical ventilation
Dysphagia	Occasional swallowing problems, no dietary adaptation required, chocking rare (<1/week)	Dietary adaptation required or chocking frequent (<1/week)	Oral nutrition not possible. Feeding tube placement. Aspiration pneumonia.
Dysarthria	No difficulties being understood	Sometimes or often asked to repeat statement	Unintelligible most of the time
Nocturnal abnormal movements/behaviors-vocalizations	Occasional (<1/week), not frequent nor intense	Frequent (at 1/week) and only sometimes intense	Almost every night (at least 5/week), continuous and/or intense (regularly waking up bedpartner or causing bedpartners to sleep in different rooms)
Insomnia [2]	Some difficulties in falling sleep, occasional nocturnal awakenings,	In between mild and severe	Important difficulties in falling sleep almost every night; or frequent/prolonged, awakenings
Excessive sleepiness [3]	Feels often sleepy but rarely falls asleep	Feels frequently sleepy and falls asleep as soon as he/she relaxes	Episodes of sudden unintended sleep in active situations (sleep attacks)
Obstructive sleep apnea [4]	Occasional, supine related snoring with apnea's or gasping (or an AHI <15);	Moderate: in between (or an AHI 15-30 without CPAP)	Continuous apnea's, independent of the posture (or AHI >30) or needs CPAP treatment
Gait difficulties and falls	Some difficulties but gait is unassisted or rare falls (< 2/month)	Gait possible with aid (cane, walker, support) or often falls (2-4/month)	Gait not possible with aid (wheelchair bound) or very often falls > 1/week
Chorea [5]	Without functional impairment	With partial-mild/moderate functional impairment	Complete/important functional impairment
Orofacial dyskinesias [5]	Without functional impairment	With partial-mild/moderate functional impairment	Complete/important functional impairment
Other movement disorders [6, 7]	Without functional impairment	With partial-mild/moderate functional impairment	Complete/important functional impairment

Cognitive impairment	Impairment appreciated by patient or caregiver without interference with the patient's ability to carry out normal activities and social interactions (or MOCA > 26)	Clinical or neuropsychological evidence of cognitive dysfunction, but minimal interference with the patient's ability to carry out normal activities and social interactions (or MOCA:18-25)	Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions (dementia; MOCA < 18)
Neuropsychiatric (psychosis, delirium)	Formed hallucination with no loss of insight. Or occasional (<1week) episodes of nocturnal confusion	Formed hallucinations with loss of insight. Or frequent (>1week) episodes of nocturnal confusion	Patient has delusions or paranoia. Or almost continuous daytime and nocturnal confusion
Oculomotor abnormalities	Slow saccades or nystagmus	Partial vertical and/or horizontal gaze limitation	Complete vertical and/or horizontal gaze palsy
Dysautonomia	Episodes of intense perspiration or urinary dysfunction	Symptomatic orthostatic hypotension, without syncope	Orthostatic hypotension with syncope, cardiac arrythmias (bradycardias or tachycardias), takotsubo syndrome
Fasciculations	Localized, intermittent, occasional.	Continuous, frequent, or intermittent but more than one body region	Fasciculations with weakness/muscle atrophy

AHI: apnea-hypopnea index; CPAP: continuous positive airway pressure; ICU: intensive care unit; MOCA: Montreal Cognitive Assessment; PSG: polysomnogram.

[1] Stridor is a high-pitched respiratory sound produced by turbulent airflow through a partially obstructed upper airway in the larynx, usually caused by a narrow glottic space. It is usually heard during inspiration, but can also be expiratory (as an example, see the audiovisual recording, see the difference with snoring, video-1).

[2] As insomnia is a prevalent symptom in the general population, a chronic history of this symptom, initiated more than 3 years before the onset of other symptoms related to anti-IgLON5 disease, should not be scored, especially if insomnia remains unchanged. Insomnia has to be scored when appears for first time, or in a case of a long-lasting history, if it significantly worsens within the previous 3 years before the development of other symptoms of anti-IgLON5 disease.

[3] As excessive sleepiness is a prevalent symptom in the general population, a chronic history of this symptom, initiated more than 3 years before the onset of other symptoms related to anti-IgLON5 disease, should not be scored, especially if excessive sleepiness remains unchanged. Excessive sleepiness must be scored when appears for first time, or in a case of a long-lasting history, if it significantly worsens within the previous 3 years before the development of other symptoms of anti-IgLON5 disease.

[4] Refers to first-ever obstructive sleep apnea with temporal relationship (within 3 years) to the onset of other symptoms of anti-IgLON5 disease. As obstructive sleep apnea is frequent in the general population, long-lasting (> 3years) previous diagnosis of obstructive sleep apnea syndrome is not scored, except if a significantly worsening of the sleep apnea occurs in relation to the development of other symptoms of anti-IgLON5 disease (within 3 years).
[5] Chorea includes limb/body dyskinetic movements, involving or not the face. Orofacial/cranial dyskinesias includes isolated orofacial chorea (if involves limb and/or body rate as chorea), myorhythmia, dystonia and myokymia.
[6] Other movement disorders include limb tremor, myoclonus or dystonia, abdominal dyskinesia, abnormal body posture (e.g antecollis-head drop, flexed trunk), stiffness/spasms, akinesia/parkinsonism, or akathisia. If more than one movement disorder, select the most disabling/severe one.
[7] For akinesia/parkinsonism: Mild: Slow movements, but full range possible. Definition: Akinesia and / or rigidity are detected in at least one body part, but the corresponding movement can be performed in the full range, Moderate: Reduced range in active movements. Definition: Akinesia and / or rigidity are detected in at least one body part, and the patient cannot voluntarily achieve the full range of movements in this body part, as would be expected for his / her age. However, the full range can be achieved passively by the examiner, Severe: Reduced range in passive movements. Definition: Akinesia and / or rigidity are detected in at least one body part, and the patient cannot voluntarily achieve the full range of movements in this body part, as would be expected for his / her age. The full range also cannot be achieved passively by the examiner.

Table 3. Demographic and clinical data of 86 patients with anti-IgLON5 disease

	Cohorts			
Variable	**Barcelona**	**GENERATE**	**TOTAL**	***p***
Patients, n	46	40	86	
External patients, n (%) [a]	35 (76)	23 (57)	58 (67)	0.07
Age at diagnosis (years) Median, range	66.5 (46-91)	64.5 (46-90)	66 (46-91)	0.29
Sex (male), n (%)	22 (48)	25 (62)	47 (55)	0.20
HLA DRB1*1001, n (%)	30/39 (77)	20/36 (56)	50/75 (67)	0.049
HLA DQB1*0501, n (%)	33/37 (89)	29/35 (83)	62/72 (86)	0.44
Diagnostic delay (months) Median, range	23 (1-108)	31 (1-135)	25 (1-156)	0.32
Chronic presentation, n (%)	30 (65)	30 (75)	60 (70)	0.36
Clinical phenotype, n (%)				
Bulbar	16 (35)	18 (45)	34 (40)	0.33
Movement disorders	10 (22)	11 (28)	21 (24)	0.53
Sleep	8 (17)	6 (15)	14 (16)	0.76
Cognitive	10 (22)	1 (3)	11 (13)	0.008
Neuromuscular	2 (4)	4 (10)	6 (7)	0.41 [F]
mRS, n (%)				
1	1 (2)	4 (10)	5 (6)	0.18 [F]
2	13 (28)	13 (33)	26 (30)	0.67
3	15 (33)	14 (35)	29 (34)	0.81
4	13 (28)	7 (18)	20 (23)	0.24
5	4 (9)	2 (5)	6 (7)	0.68 [F]

mRS: modified Rankin scale. [a] Externals patients: patients seen at other institutions different from the Hospital Clinic, Barcelona and St. Josef Hospital, Bochum, with clinical data collected through a standardized questionnaire filled by the treating physicians. [F] Fisher test used. *P* values less than 0.05 were considered significant.

Table 4. Anti-IgLON5 disease composite score (ICS) and partial score of the five domains

	Total N =86	**Barcelona Cohort** N = 46	**GENERATE Cohort** N = 40	**p**	**Internal patients** N = 28	**External patients**[a] N = 58	***p***
Total ICS Median(range)	15 (2-31)	18 (2-31)	12 (4-23)	<0.001	15 (4-24)	14 (2-31)	0.96
Partial scores, median (range)							
Bulbar	3 (0-14)	3 (0-14)	2.5 (0-12)	0.80	3 (0-11)	3 (0-14)	0.59
Sleep	4 (0-11)	5 (0-11)	2 (0-11)	0.02	5.5 (0-11)	3 (0-11)	0.03
Movement disorders	2 (0-9)	3 (0-9)	1 (0-8)	0.006	1 (0-7)	2 (0-9)	0.44
Cognition	1 (0-12)	1 (0-12)	1 (0-6)	0.05	0.5 (0-12)	1 (0-12)	0.25
Other symptoms	2 (0-5)	2 (0-5)	2 (0-5)	0.15	1.5 (0-5)	2 (0-5)	0.77

[a] Externals patients: patients seen at other institutions different from the Hospital Clinic, Barcelona and St. Josef Hospital, Bochum. *P* values less than 0.05 were considered significant.

Table 5. Anti-IgLON5 disease composite score (ICS) and partial scores according to clinical phenotypes

		Clinical phenotype				
	Total (N=86)	**Bulbar** (N= 34)	**Movement disorders** (N= 21)	**Sleep** (N= 14)	**Cognitive** (N= 11)	**Neuromuscular** (N= 6)
ICS Median (range)	15 (2-31)	15.5 (4-31)	14 (2-25)	15 (6-24)	12 (6-25)	8.5 (1-14)
Phenotype	**Partial scores** [median (range)]					
Bulbar	3 (0-14)	8.5 (1-14)	2 (0-9)	3.5 (1-10)	0 (0-4)	0.5 (0-3)
Sleep	4 (0-11)	3.5 (0-10)	3 (0-7)	9 (2-11)	2 (0-9)	1.5 (0-4)
Movement disorders	2 (0-9)	1 (0-9)	4 (1-9)	2 (0-5)	2 (0-7)	0 (0-2)
Cognition	1 (0-12)	0 (0-6)	1 (0-7)	1 (0-4)	8 (1-12)	1 (0-2)
Other	2 (0-5)	2 (0-5)	2 (0-5)	1(0-4)	0 (0-5)	2 (1-4)

Figure Legends

Figure 1. A. Distribution of the anti-IgLON5 disease composite total score (ICS). B and C: Distribution of the ICS in the Barcelona (BCN) and GENERATE cohorts respectively. D. Distribution of partial score for each domain.

Figure 2. A. Anti-IgLON5 disease composite total score (ICS) and modified Rankin Scale (mRS). B. Anti-IgLON5 disease composite total score (ICS) by clinical phenotype (the red line represents the median for each phenotype).

Development of a composite score for the assessment of anti-IgLON5 disease

Supplemental material

e-Table 1. Demographic and general clinical data of internal and external patients

	Internal	**External**	***p***
Patients, n	28	58	
Clinic Barcelona, n (%) **GENERATE, n (%)**	11 (24) 17 (42)	35 (76) 23 (57)	0.07
Age at diagnosis (years) Median, range	64.5 (46-90)	66.0 (46-91)	0.61
Gender (male), n (%)	17 (61)	30 (52)	0.43
HLA DRB1*1001, n (%)	18/28 (64)	32/47 (68)	0.74
HLA DQB1*0501, n (%)	24/28 (86)	38/44 (86)	0.94
Diagnostic delay (months) Median, range	36 (1-144)	24 (1-156)	0.62
Chronic presentation, n (%)	19 (68)	41 (71)	0.79
Clinical phenotypes, n (%) Bulbar Movement disorders	 12 (43) 4 (14)	 22 (38) 17 (29)	 0.66 0.13

Sleep	7 (25)	7 (12)	0.13
Cognitive	4 (14)	7 (12)	0.77
Neuromuscular	1 (4)	5 (9)	0.66
Modified Rankin score, n (%)			
1	2 (7)	3 (5)	0.66
2	12 (43)	14 (24)	0.08
3	7 (25)	22 (38)	0.23
4	6 (21)	14 (24)	0.78
5	1 (4)	5 (9)	0.66

e-Table 2. Missing values and distribution of the different scores for each symptom

		Missing values n (%)[1]	**0 (absent)** n (%)[2]	**1 (mild)** n (%)[2]	**2 (moderate)** n (%)[2]	**3 or 6 (severe)** n (%)[2]
Bulbar	Stridor	21 (24)	37 (57)	3 (5)	15 (23)	10 (15)
	Central hypoventilation	2 (2)	59 (70)	1 (1)	16 (19)	8 (10)
	Dysphagia	0 (0)	27 (31)	30 (35)	23 (27)	6 (7)
	Dysarthria	1 (1)	32 (38)	37 (44)	12 (14)	4 (5)
Sleep	Abnormal sleep movements/behaviors	1 (1)	26 (31)	17 (20)	20 (23)	22 (26)
	Insomnia	26 (30)	28 (47)	5 (8)	20 (33)	7 (12)
	Excessive sleepiness	3 (3)	42 (51)	18 (22)	16 (19)	7 (8)
	Obstructive sleep apnea	22 (25)	21 (33)	10 (16)	13 (20)	20 (31)
Mov dis.	Gait difficulties and falls	0 (0)	30 (35)	30 (35)	18 (21)	8 (9)
	Chorea, n (%)	0 (0)	69 (80)	9 (11)	6 (7)	2 (2)
	Orofacial dyskinesias	0 (0)	61 (71)	15 (17)	8 (9)	2 (2)
	Other movement disorders	0 (0)	53 (62)	26 (30)	4 (5)	3 (3)
Cog.	Cognitive impairment	1 (1)	45 (53)	26 (31)	5 (6)	9 (11)

	Neuropsychiatric symptoms	0 (0)	60 (70)	10 (12)	11 (13)	5 (6)
Other	Oculomotor abnormalities	0 (0)	37 (43)	18 (21)	26 (30)	5 (6)
	Dysautonomia	0 (0)	49 (57)	29 (34)	3 (3)	5 (6)
	Fasciculations	0 (0)	71 (83)	6 (7)	8 (9)	1 (1)

[1]The denominator for this % includes observed plus lost items. *[2] Lost items excluded*

	e-Table 3. Missed data with number of items lost and distribution of the scores for each symptom by center										
		Lost items		**0 (absent)**		**1 (mild)**		**2 (moderate)**		**3 or 6 (severe)**	
		BCN	**GENERATE**	**BCN**	**GENERATE**	**BCN**	**GENERATE**	**BCN**	**GENERATE**	**BCN**	**GENERATE**
Bulbar	**Stridor, n (%)**	**2 (4)**	**19 (47)**	24 (54)	13 (62)	3 (7)	0 (0)	9 (20)	6 (29)	8 (18)	2 (9)
	Central hypoventilation, n (%)	**0 (0)**	**2 (5)**	36 (78)	23 (60)	0 (0)	1 (3)	2 (4)	14 (37)	8 (17)	0 (0)
	Dysphagia, n (%)	**0 (0)**	**0 (0)**	14 (30)	13 (32)	15 (33)	15 (37)	15 (33)	8 (20)	2 (4)	4 (10)
	Dysarthria, n (%)	**1 (2)**	**0 (0)**	15 (33)	17 (42)	24 (53)	13 (32)	6 (13)	6 (15)	0 (0)	4 (10)

Sleep	**Abnormal sleep movts/behaviors, n (%)**	**1 (2)**	**0 (0)**	11 (24)	15 (37)	8 (18)	9 (22)	15 (33)	5 (12)	11 (24)	11 (27)
	Insomnia, n (%)	**2 (4)**	**24 (60)**	20 (45)	8 (50)	4 (9)	1 (6)	15 (34)	5 (31)	5 (11)	2 (12)
	Excessive sleepiness, n (%)	**3 (6)**	**0 (0)**	16 (37)	26 (65)	14 (33)	4 (10)	11 (26)	5 (12)	2 (5)	5 (12)
	Obstructive sleep apnea, n (%)	**1 (2)**	**21 (52)**	14 (31)	7 (37)	8 (18)	2 (10)	9 (20)	4 (21)	14 (31)	6 (32)
Mov dis	**Gait difficulties and falls, n (%)**	**0 (0)**	**0 (0)**	15 (33)	15 (37)	16 (35)	14 (35)	8 (17)	10 (25)	7 (15)	1 (2)
	Chorea, n (%)	**0 (0)**	**0 (0)**	33 (72)	36 (90)	7 (15)	2 (5)	5 (11)	1 (2)	1 (2)	1 (2)
	Orofacial dyskinesias, n (%)	**0 (0)**	**0 (0)**	30 (65)	31 (77)	12 (26)	3 (7)	2 (4)	6 (15)	2 (4)	0 (0)

	Other movement disorders, n (%)	**0 (0)**	**0 (0)**	21 (46)	32 (80)	21 (46)	5 (12)	3 (6)	1 (2)	1 (2)	2 (5)
Cogn.	**Cognitive impairment, n (%)**	**0 (0)**	**1 (2)**	24 (52)	21 (54)	11 (24)	15 (38)	2 (4)	3 (8)	9 (20)	0 (0)
	Neuropsychiatric symptoms, n (%)	**0 (0)**	**0 (0)**	25 (54)	35 (87)	8 (17)	2 (5)	9 (20)	2 (5)	4 (9)	1 (2)
Other	**Oculomotor abnormalities, n (%)**	0 (0)	0 (0)	19 (41)	18 (45)	9 (20)	9 (22)	16 (35)	10 (25)	2 (4)	3 (7)
	Dysautonomia, n (%)	0 (0)	0 (0)	19 (41)	30 (75)	22 (48)	7 (17)	1 (2)	2 (5)	4 (9)	1 (2)
	Fasciculations, n (%)	0 (0)	0 (0)	39 (85)	32 (80)	2 (4)	4 (10)	4 (9)	4 (10)	1 (2)	0 (0)

eTable 4. Internal consistency for the total composite score and subscore domains (Cronbach's alpha)

	Number of items	**Number of patients analyzed**	**Cronbach's alpha coefficient**
IgLON5 composite score	17	56	0.308
Partial scores			
Bulbar symptoms	4	62	0.526
Sleep symptoms	4	57	0.640
Movement disorders	4	86	0.268
Cognition	2	85	0.569
Other symptoms	3	86	0.141

Internal consistency is considered acceptable when the Cronbach's alpha coefficient is > 0.7.

e-Table 5. Inter-rater and intra-rater (re-test) reliability (intraclass coefficient) for the anti-IgLON5 disease composite score and partial score domains.

	Inter-rater reliability **ICC**	**Intra-rater reliability** **ICC**
ICS	0. 973 (0.925-0.990)	0.997 (0.992-0.999)
Partial scores		
Bulbar symptoms	0.962 (0.906-0.985)	0.995 (0.986-0.998)
Sleep symptoms	0.963 (0.863-0.987)	0.987 (0.967-0.995)
Movement disorders	0.940 (0.847-0.976)	1.0
Cognition	0.975 (0.937-0.990)	0.996 (0.989-0.998)
Other symptoms	0.925 (0.808-0.970)	1.0

Intraclass coefficient (ICC) (95% confidence intervals)

Values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively.

e-Table 6. Inter-rater and intrarater (re-test) agreement for each items (Cohen's kappa coefficient)

		Inter-rater agreement (Cohen's kappa)	**Intra-rater o re-test agreement (Cohen's kappa)**
Bulbar	Stridor	0.88	0.86
	Central hypoventilation	0.44	1.0
	Dysphagia	0.48	0.92
	Dysarthria	0.74	1.0
Sleep	Abnormal sleep movements/behaviors	0.55	0.86
	Insomnia	0.48	0.88
	Excessive sleepiness	0.61	0.82
	Obstructive sleep apnea	0.54	0.92
Mov. disord	Gait difficulties and falls	0.69	1.0
	Chorea	0.51	1.0
	Orofacial dyskinesias	0.49	1.0
	Other movement disorders	0.45	1.0

Cog.	Cognitive impairment	0.59	0.92
	Neuropsychiatric symptoms	0.57	0.79
Other	Oculomotor abnormalities	0.54	1.0
	Dysautonomia	0.61	1.0
	Fasciculations	0.55	1.0

Values ≤ 0 indicate no agreement; 0.01–0.20: none to slight; 0.21–0.40: fair; 0.41– 0.60: moderate; 0.61–0.80: substantial, and 0.81–1.00: almost perfect agreement.