Anti-IgLON5 Disease
A New Bulbar-Onset Motor Neuron Mimic Syndrome

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Abstract

Objective
To expand the spectrum of anti-IgLON5 disease by adding 5 novel anti-IgLON5–seropositive cases with bulbar motor neuron disease-like phenotype.

Methods
We characterized the clinical course, brain MRI and laboratory findings, and therapy response in these 5 patients.

Results
Patients were severely affected by bulbar impairment and its respiratory consequences. Sleep-related breathing disorders and parasomnias were common. All patients showed clinical or electrophysiologic signs of motor neuron disease without fulfilling the diagnostic criteria for amyotrophic lateral sclerosis. One patient regained autonomy in swallowing and eating, possibly related to immunotherapy.

Conclusion
IgLON5 disease is an important differential diagnosis to evaluate in patients with bulbar motor neuron disease-like phenotype and sleep disorders. There is need for a deeper understanding of the underlying pathobiology to determine whether IgLON5 disease is an immunotherapy-responsive condition.

*These authors contributed equally to this work.

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Glossary

AHI = apnea-hypopnoea-index; ALS = amyotrophic lateral sclerosis; ASV = adaptive servo-ventilation; CPAP = continuous positive airway pressure; FOIS = Functional Oral Intake Scale; OSA = obstructive sleep apnea; PEG = percutaneous endoscopic gastrostomy; PSG = polysomnography.

Patients presenting with sleep apnea, REM-sleep behavior disorder or non-REM parasomnia, and stridor who are seropositive for anti-IgLON5 antibodies have been first described in 2014. Since then, more than 60 cases with anti-IgLON5 disease have been reported. The function of the IgLON5 protein, a neuronal cell adhesion molecule, and the pathomechanism of anti-IgLON5 antibody-associated diseases are still insufficiently understood. Neuropathologic postmortem findings of a few cases include gliosis, neuronal loss, and neuronal agglomeration of hyperphosphorylated tau protein in areas correlating with the clinical deficits such as signs of dysfunction of the brainstem, tegmentum, hypothalamus and hippocampus areas, and to a lesser extent, anterior horns of the spinal cord.

Whether anti-IgLON5 antibodies directly cause neuronal dysfunction and degeneration or only are produced secondary to a neurodegenerative process is unclear. The strong association with HLA-DRB1*10:01 and HLA-DQB1*05:01 alleles suggests an autoimmune pathogenesis. Among anti-IgLON5 antibodies, the noncomplement-fixing IgG4 subclass predominates over IgG1, but the latter can induce internalization of IgLON5 in vitro. Previous case reports described patients with (1) sleep behavior abnormalities, (2) a progressive supranuclear palsy-like phenotype, (3) a bulbar syndrome, and (4) cognitive decline with or without chorea. In addition, Wenninger, Honorat, and colleagues reported the presence of motor-neuron signs (e.g., fasciculations, atrophy, and spasticity) in some patients with anti-IgLON5 disease. Bulbar symptoms combined with these signs can lead to suspect a bulbar-onset motor-neuron disease. Here, we present 5 anti-IgLON5-seropositive patients with predominant bulbar dysfunction including severe laryngeal stridor causing episodes of respiratory failure, different types of sleep-related breathing disorders, and parasomnia and dysphagia that received immunotherapy and partially improved or stabilized during the disease course. Patients with IgLON5-associated disease were identified by the clinical phenotype and polysomnography (PSG) findings. They were referred to the Neuromuscular Center, University Hospital Zurich, Switzerland, between August 2017 and November 2019 for bulbar symptoms and with the question whether there were further signs of motor neuron disease. This observational study should alert physicians to consider anti-IgLON5 disease as differential diagnosis of a clinical phenotype resembling bulbar-onset motor neuron disease.

Methods

Patient Consents

Informed consent was obtained from all 5 patients in this clinical case series.

Data Availability

Anonymized data including laboratory results, imaging, and electrophysiologic and sleep testing data will be shared by request from any qualified investigator.

Case Descriptions

Clinical Findings

Five men aged 52–77 years (median: 70) at diagnosis presenting with recurrent respiratory distress and progressive neurogenic dysphagia as cardinal symptoms were referred because of suspicion of bulbar-onset motor neuron disease. The time from onset of symptoms to diagnosis of anti-IgLON5 disease ranged from 7 months to 3.5 years (median 2 years). None of them had a history of autoimmune disease or cancer. The demographics and clinical features are described in detail in tables 1 and 2. Two patients (patients 1 and 3) presented with recurrent acute hypercapnic respiratory failure because of laryngeal dysfunction requiring intubation and subsequent tracheotomy. Patient 1 had been diagnosed with obstructive and central sleep apnea 3 years earlier, but both continuous positive airway pressure (CPAP) and adaptive servoventilation (ASV) were unsuccessful. Episodes of acute dyspnea accompanied by stridor worsened and led to repeated tracheal intubations. Furthermore, he developed dysarthria and dysphagia over the previous 2 years. Patient 3 had a 9-month history of severe dyspnea attacks resulting in acute hypercapnic respiratory failure that were also attributed to laryngeal dysfunction. Three patients were referred mainly because of progressive dysphagia with weight loss, tongue dysmotility, and dysarthria for 7 months (patient 5) to 1.5–2.5 years (patient 4 and 2). In addition, patients 2 and 4 complained of episodes of breathing difficulties and disturbed sleep with daytime sleepiness (patient 2) or recurrent nocturnal tongue biting (patient 4). Patients 1, 2, 4, and 5 received nocturnal positive airway pressure therapy (CPAP, ASV, or bilevel positive airway pressure) 4–10 years before the diagnosis of anti-IgLON5 disease. In patients 1, 2, 4, and 5, clinical features of motor neuron involvement were documented including an increased jaw jerk reflex and muscle spasticity and occasional muscle fasciculations in tongue, arm and thigh muscles, facial myokymia, and cramps.

Investigations

All 5 patients had serum antibodies against IgLON5 (table 1), 2 also in the CSF. The serum anti-IgLON5 antibodies belonged to the IgG1 (patients 2–5) and IgG4 isotype (all 5 patients). By contrast, when we retrospectively tested archived serum and CSF samples of 5 male patients diagnosed
previously with amyotrophic lateral sclerosis (ALS) and identified by a search in our neuromuscular center database, they were negative for anti-IgLON5 antibodies (ALS “clinically possible” or “definite” according to the Awaji criteria,10 age range: 57–75 years; 4 with bulbar symptoms). There were no inflammatory changes in the CSF of patients

### Table 1 Demographics, Initial Findings, HLA-Alleles, Serology, and Immunotherapy

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<td><strong>Demographics</strong></td>
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<tr>
<td>Age at diagnosis</td>
<td>74 years</td>
<td>52 years</td>
<td>77 years</td>
<td>63 years</td>
<td>70 years</td>
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<tr>
<td>Gender</td>
<td>Male</td>
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<tr>
<td>Origin</td>
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<td>Sri Lankan</td>
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<td>Swiss</td>
<td>Italian</td>
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<tr>
<td><strong>Time from onset to diagnosis</strong></td>
<td>Approx. 2 years after onset of dysarthria and 6 months after onset of acute respiratory crises</td>
<td>Approx. 3.5 years after onset of hoarseness and 14 months after onset of attacks of dyspnea</td>
<td>Approx. 2 years after onset of hoarseness and 14 months after onset of attacks of dyspnea</td>
<td>Approx. 1.5 years after onset of dysphagia</td>
<td>Approx. 7 months after onset of dysphagia</td>
</tr>
<tr>
<td><strong>Symptoms at onset</strong></td>
<td>OSA</td>
<td>Dysphagia</td>
<td>Hoarseness</td>
<td>Episodes of dyspnea, OSA + parasomnia</td>
<td>OSA</td>
</tr>
<tr>
<td><strong>Symptoms at diagnosis</strong></td>
<td>Same as above + dysphagia dysarthria, stridor and episodes of dyspnea</td>
<td>Same as above + dysphagia dysarthria, OSA, increased daytime sleepiness</td>
<td>Same as above + episodes of dyspnea, dysphagia</td>
<td>Same as above + dysphagia</td>
<td>Same as above + “swollen tongue,” dysphagia, dysarthria, and dysgeusia</td>
</tr>
<tr>
<td><strong>Reason for referral to neurologist</strong></td>
<td>Unclear bulbar symptoms</td>
<td>Progressive dysphagia</td>
<td>Unclear difficulties with voice and swallowing</td>
<td>Progressive dysphagia</td>
<td>Progressive dysphagia</td>
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<tr>
<td><strong>HLA-allele</strong></td>
<td>HLA-DRB1*10:01</td>
<td>-/-</td>
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<tr>
<td><strong>Anti-IgLON5</strong></td>
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<tr>
<td>In serum</td>
<td>Positive (1:1,000)</td>
<td>Positive (&gt;1:1,000)</td>
<td>Positiveb</td>
<td>Positive (&gt;1:1,000)</td>
<td>Positive (1:320 and 1:1,000)</td>
</tr>
<tr>
<td>In CSF</td>
<td>Negativea</td>
<td>Positive (&gt;1:100)</td>
<td>Not analyzed</td>
<td>Positive (1:32)a</td>
<td>Negativea</td>
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<tr>
<td>IgG1c</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
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<tr>
<td>IgG4c</td>
<td>Positive</td>
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<td><strong>Immunotherapy</strong></td>
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<td>Period between onset of symptoms and beginning of immunotherapy</td>
<td>7 months after onset of episodes of acute dyspnea</td>
<td>Approx. 45 months after onset of dysphagia</td>
<td>15 months after onset of attacks of dyspnea</td>
<td>Approx. 20 months after onset of dysphagia</td>
<td>Approx. 7 months after onset of dysphagia</td>
</tr>
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<td>Compound, duration, dose</td>
<td>Mercaptopurine (75 mg/d)</td>
<td>IV methylprednisolone 1g/d, 5 consecutive days PEX, 5 cycles, every other day Rituximab (375 mg/m² body surface, 1x)</td>
<td>PEX, 3 cycles, every other day IVIG, 2 cycles (0.4 g/kg/d for 5 days, monthly interval) Rituximab (375 mg/m² body surface, 2x)</td>
<td>2× IV methylprednisolone 1g/d, 5 consecutive days 2× PEX, 5 cycles, every other day Rituximab (375 mg/m² body surface, 1x)</td>
<td>IV methylprednisolone 1g/d, 5 consecutive days PEX, 5 cycles, every other day Rituximab (375 mg/m² body surface, 1x)</td>
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<tr>
<td>Response to immunotherapy</td>
<td>Partial improvement (PEG removed, re-tracheostomy necessary)</td>
<td>Persistent bulbar symptoms (tracheostomy recommended but refused by patient)</td>
<td>Partial improvement (swallowing), (tracheostomy)</td>
<td>Persistent dysphagia (PEG, recurrent attacks of acute dyspnea (tracheostomy))</td>
<td>Persistent dysphagia, (PEG and tracheostomy)</td>
</tr>
<tr>
<td>mRS at last visit</td>
<td>2</td>
<td>2</td>
<td>2</td>
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Abbreviations: IVIG = IV immunoglobulins, mRS = modified Rankin Scale; PEG = percutaneous endoscopic gastrostomy; PEX = plasma exchange. Cell-based immunofluorescence assays performed at the Dep. of Clinical Immunology, University Hospital Zurich, at the Dep. of Neurology, Medical University of Innsbruck, Austria, analyzed by Euroimmun, Lübeck, Germany.
1–5 except mild-to-moderate elevated CSF protein (no intrathecal IgG synthesis in 3 of 5 CSF samples analyzed). Brain and spinal cord MRI findings of all 5 patients were unremarkable. Serologic tests were negative for HIV, Borrelia burgdorferi, Treponema pallidum and acetylcholine receptor, muscle specific tyrosine kinase (MuSK), titin, lipoprotein receptor-related protein 4, and cN-A (Mup44) antibodies. Creatine kinase values were not significantly elevated. Analysis of phosphorylated neurofilament heavy chain (pNF-H), a proposed diagnostic biomarker for ALS, showed marginally positive results in 1 of 5 of our patient serum samples and one of one analyzed CSF samples (patient 4; analyzed by Euroimmun, Lübeck, Germany). Three of the 5 patients expressed HLA-DRB1*10:01 in combination with HLA-DQB1*05:01 alleles, and one patient expressed HLA-DQB1*05:01 without HLA-DRB1*10:01. Of the 2 patients negative for HLA-DRB1*10:01, patient 3 was homozygous for HLA-DRB1*03:01 and patient 1 was HLA-DRB1*01:01 and HLA-DRB1*04:04. EMG revealed subtle pathologic spontaneous activity and chronic neurogenic changes in different regions including the masseter, limb, and even thoracic paravertebral muscles in all 5 patients, individually not fulfilling the Awaji-Shima consensus criteria for ALS10 (table 2). A disturbed sleep architecture with an alpha-delta pattern was detected in the PSG of patient 1 who had a history of parasomnia (table 3). Respiratory moaning, inspiratory flow limitations with cyclic oxygen desaturations, and central apneas (apnea-hypopnea index [AHI] 16/h), inspiratory stridor, snoring, and increased periodic limb movements were noted. The PSG of patient 2 demonstrated a markedly reduced sleep efficiency and REM sleep behavior disorder. A respiratory polygraphy with capnography off CPAP confirmed severe obstructive sleep apnea (OSA) and demonstrated episodes of sleep-related hypoventilation and inspiratory stridor. The PSG of patient 4 revealed a markedly fragmented sleep profile with many arousals (rarely associated with periodic limb movements), REM sleep behavior disorder, but showed no residual sleep-disordered breathing or stridor on noninvasive ventilation. Patient 3’s PSG did not reveal any relevant breathing disorder or stridor but increased periodic limb movements in part associated with arousals. The PSG of patient 5 on ASV for treatment-emergent central sleep apnea demonstrated increased periodic limb movements and REM-sleep behavior disorder. A cardiorespiratory polygraphy after tracheotomy revealed mild central sleep apnea (AH1 14/h). A video fluoroscopic and endoscopic swallowing examination was performed in all 5 patients and showed signs of salivary and silent aspiration and laryngeal penetration. The lowest FOIS (Functional Oral Intake Scale) value reached was I-II (patients 1, 4, and 5) (level I: nothing by mouth and level II: tube feeding with minimal attempts of oral feeding), and thus, a percutaneous endoscopic gastrostomy (PEG) was inserted. The ability of oral intake in patient 2 and 3 were evaluated as FOIS value V (total oral intake of multiple consistencies requiring special preparations) or V to VI (total oral intake with no special preparation, but must avoid specific foods and liquid items), respectively. All patients underwent fiberoptic evaluation/laryngoscopy by ENT/phonation specialists demonstrating velopharyngeal insufficiency and functional laryngeal impairment (e.g., bilaterally impaired vocal cord function and paresis) (table 2).

**Follow-Up**

All 5 patients received immunotherapy that was started between 7-15 months after onset of recurrent respiratory failure (patients 1 and 3) and approximately 7 months to 3.5 years after gradual onset of dysphagia (patients 5, 4, and 2) (table 1). One patient improved (patient 1) under Mercaptopurine (up to 75 mg/d p.o.) as maintenance immunotherapy. Mercaptopurine was chosen based on the personal experience and preference of his treating neurologist back at home. On a follow-up visit, dysphagia was only mild, and it was planned to remove the PEG. Physical activity and exertional dyspnea improved. The tracheostoma was removed, but retracheotomy was necessary shortly after because of an acute dyspnea attack at night. Patient 2 received a steroid pulse therapy, plasma exchange, and a B cell depleting maintenance treatment with rituximab, but anti-IgLON5 antibody levels remained high. Nevertheless, he was doing well in the past 6 months. Patient 3 received plasma exchange, followed by IV immunoglobulins and rituximab. At follow-up visits, he reported improved swallowing and no further weight loss. He still has a tracheostoma, but there were no respiratory crisis and emergency admissions to the hospital since the first plasma exchange 11 months ago. Despite initiation of an IV methylprednisolone pulse therapy, patient 4 had to be hospitalized repeatedly because of acute episodes of laryngospasm and acute respiratory failure requiring intubation and additional plasmapheresis. The patient finally consented to a tracheostomy and PEG tube placement. After another IV methylprednisolone pulse and rituximab therapy, patient 4 still suffers from severe dysphagia, and recurrent attacks of acute dyspnea and serum anti-IgLON5 antibodies are still positive. Patients 5’s immunotherapy was started with an IV methylprednisolone pulse, plasma exchange sessions, and continues with rituximab. So far, he is still dependent on the PEG tube.

**Discussion**

The initial symptoms suggested bulbar onset motor neuron disease further supported by the fact that all 5 patients demonstrated signs of spasticity, hyperreflexia, mild atrophy and limb weakness, and fasciculations of the tongue and peripheral muscles. Disease duration since diagnosis spanned from 3 to 19 months. It has been reported that IgLON cell surface proteins are expressed also outside of the CNS and that peripheral involvement in anti-IgLON5 syndromes can occur.5,6 Altogether, our patients did not fulfill diagnostic criteria for clinically definite ALS10 because there was no typical progressive spread to other body regions. ALS patients are at increased risk for sleep-related breathing disorders, particularly OSA and nocturnal hypoventilation. However, the sleep disturbances associated with anti-IgLON5 disease such as a short REM onset
latency, a high proportion of REM sleep, and a low proportion of slow wave sleep and parasomnias including vocalizations, limb movements, and gesturing do usually not occur. Recently, patient populations with the classical tauopathy progressive supranuclear palsy or isolated OSA have been tested negative for IgLON5 autoimmunity.\textsuperscript{1,11,12} Our retrospective analysis of serum and CSF specimens of 5 additional patients with ALS identified by a search in our neuromuscular database revealed no reactivity against IgLON5 and supports results that these antibodies are highly specific.\textsuperscript{1} Previous data suggest that patients with anti-IgLON5 disease who are not treated or only treated with systemic corticosteroids have a higher mortality.\textsuperscript{3} Patients with a bulbar or motoneuron-like phenotype might have a worse response to immunotherapy,\textsuperscript{2,6,7} but case

| Table 2 Bulbar and Motor-Neuron Signs, EMG, and Other Neurological Features |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Case 1**  | **Case 2**  | **Case 3**  | **Case 4**  | **Case 5**  |
| **Bulbar symptoms** | Dysphagia dysarthria, episodes of dyspnea | Dysphagia, dysarthria | Hoarseness, episodes of dyspnea, dysphagia | Episodes of dyspnea, dysphagia | “Swollen tongue,” dysphagia, dysarthria |
| **Stridor** | Yes | Yes | Yes | — | No |
| **Laryngeal dysfunction** | Bilateral vocal cord paresis, dysynchrony, paradoxical movements | Symmetric mobility of vocal cords | Severe bilateral vocal cord paresis | Bilateral vocal cord paresis | Bilateral vocal cord paresis, swelling of arytenoid mucosa |
| **Tracheotomy** | Yes | — | Yes | Yes | Yes |
| **Motor signs** | | | | | |
| **Limbs, cranial (except tongue)** | Increased masseter reflex activity, leg spasticity, arm and leg muscles' fasciculations, mild leg muscles' atrophy | Increased masseter reflex activity, perioral myokymia, | None | Perioral fasciculations | None |
| **Tongue** | Slightly reduced tongue motility/ strength, no atrophy or fasciculations | Reduced tongue motility/ strength, no atrophy, but fasciculations | None | Slightly reduced tongue motility/ strength, no atrophy or fasciculations | Severe tongue palsy, feeling of having a “swollen tongue,” fasciculations |
| **EMG study** | Fibs-sw (anterior tibial, vastus lateralis), FPs (biceps brachii) and CRD (masseter), and chronic neurogenic changes | Fibs (tongue, anterior tibial), CRD, doublets (FDI), and chronic neurogenic changes | Fibs-sw, CRD in limb muscles, and signs of chronic denervation | A few FPs (masseter and FDI), chronic neurogenic changes in 1 muscle (FDI) | A few FPs (biceps, FDI), mild chronic neurogenic changes (FDI) |
| **Gait instability, movement disorder** | None (walks more than 1 hour in the mountains) | Reduced endurance (needs to rest every 10 minutes when walking), rare falls | None; 6 minutes walking test without aid: 560 m | Slightly unsteady gait, no falls, 6 minutes walking test without aid: 420 m | None; 6 minutes walking test without aid: 400 m |
| **Cognitive impairment, neuropsychiatric symptoms** | None reported | Fatigue, difficulties concentrating, and reduced drive and executive functions (neuropsychological testing). Family reports occasional memory disturbances, confusion, and visual hallucinations | None reported | Recurrent depressive disorder, “burnout syndrome,” reduced impulse control and semantic fluency (neuropsychological testing) | None reported |
| **Dysautonomia** | Episodes of tachycardia (catheter ablation for re-entrant tachycardia), tachyarrhythmia, torsade-de-pointes, AV-block 3rd degree | None reported | Nycturia (BPH), obstipation, night sweats, during episodes of dyspnea: Palpitations, NSTEMI requiring coronary artery stenting, and DD Takotsubo cardiomyopathy | Signs of BPH, erectile dysfunction, episodes of tachycardia and palpitations, 24 hours ECG: normal heart rhythm, 71–149 beats/min | Hyperhidrosis, no signs of orthostatic hypotension (schelling test) |

Abbreviations: BPH = benign prostatic hyperplasia; BPH = benign prostatic hyperplasia; CRD = complex repetitive discharges; DD = differential diagnosis; Fibs-sw = fibrillation and sharp waves; FPs = fasciculation potentials; FDI, first dorsal interosseus muscle; NSTEMI = Non-ST segment elevation myocardial infarction.
numbers are too small to draw definite conclusions. Partial and transient improvements of symptoms could also be related to spontaneous fluctuations during the natural course of the illness. In our study, 2 of 5 patients (patients 1 and 3) demonstrated improved swallowing-related quality of life, weight status, and physical activity under immunotherapy, but laryngeal dysfunction was persistent and required long-term tracheostomy. Of note, patient 1 who fully recovered from dysphagia differed not only in the point of immune medication but also HLA-status (presence of HLA-DQB1*05:01 without HLA-DRB1*10:01) and absence of anti-IgLON5 antibody of the IgG1 subclass. The potential impact of certain immune phenotypes is presently highly speculative but will hopefully be examined by larger, collaborative efforts in the future.

Taken together, anti-IgLON5 disease with bulbar syndrome is an uncommon but important diagnostic consideration for neurologists, ear nose throat, respiratory, and sleep specialist in cases of suspected bulbar onset ALS. Antibody testing should be considered in patients with stridor, acute dyspnea attacks due to upper airway dysfunction early during the disease course, OSA, a prominent sleep disorder and severe dysphagia even without inflammation in MRI, and CSF studies. Our case series has limitations because it is

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<td><strong>Stridor during sleep study</strong></td>
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<td><strong>ODI (events/hr)</strong></td>
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<td><strong>Summary of sleep abnormalities</strong></td>
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Abbreviations: AHI = Apnea-hypopnea-index; ASV = adaptive servo-ventilation; BiPAP = bilevel positive airway pressure ventilation; CPAP = continuous positive airway pressure; CRD: complex repetitive discharges; CSA = central sleep apnea; Fibs-sw: fibrillation and sharp waves; FDI = first dorsal interosseus muscle; FPs = fasciculation potentials; NREM = Non-rapid eye movement; ODI = oxygen desaturation-index; OSA = obstructive sleep apnea; PAP = positive airway pressure; PLMI = periodic limb movement index; PSG = polysomnography; RP = respiratory polygraphy.
retrospective and involves a small number of patients. Whether early recognition and immune intervention alter disease progressions remains to be determined. Interdisciplinary management and care including otolaryngologists and pulmonologists is crucial to reduce the risk of respiratory failure or sudden death. Although new cases are emerging, additional mechanistic studies will be important to understand the immune process and pathophysiology underlying this disorder.

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Disclosure
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/NN for full disclosures.

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Appendix Authors

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<th>Contribution</th>
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<tr>
<td>Jana Werner, MD</td>
<td>University Hospital Zurich, Department of Neurology</td>
<td>Acquisition of clinical data and drafting of the manuscript</td>
</tr>
<tr>
<td>Iljias Jelic, MD</td>
<td>University Hospital Zurich, Department of Neurology</td>
<td>Data interpretation and drafting and revision of the manuscript</td>
</tr>
<tr>
<td>Esther Irene Schwarz, MD</td>
<td>University Hospital Zurich, Department of Pulmonology and Sleep Disorders Center</td>
<td>Data analysis and interpretation and revision of the manuscript</td>
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References
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