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Motor-neuron-disease-like phenotype associated with IgLON5 disease

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Abstract

A growing spectrum of neurological manifestations are being recognized in association with IgLON5 autoimmunity, including recent reports of motor-neuron-disease-like phenotype. Here we describe four cases of IgLON5 autoimmunity with motor neuron involvement and evaluate an additional 109 probable or definite amyotrophic lateral sclerosis cases seen in our neuromuscular clinic for IgLON5-IgG seropositivity. The presence of parasomnias, vocal cord dysfunction or hyperkinetic movements in a patient with motor-neuron-disease-like phenotype should prompt evaluation for IgLON5-IgG autoantibodies. Recognition and treatment of this autoimmune disease with immunosuppressive agents may bring about significant neurological improvement in a minority of cases.

Keywords

IgLON5 autoimmunity; Motor neuron disease; Amyotrophic lateral sclerosis

Introduction

IgLON5 autoimmunity is presumed to be an antibody-mediated disorder, first described in 2014 [1, 2]. While sleep abnormalities are most frequently seen, other associated central nervous system (CNS) manifestations have been described [3–5]. Recently, a motor-neuron-disease (MND)-like phenotype has been described as a manifestation of IgLON5 disease

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[6, 7]. Supporting these clinical observations, neuropathological studies suggest evidence of anterior horn involvement albeit to a lesser extent than the CNS in IgLON5 autoimmunity [8]. Here, we share our experience of MND-like phenotype in patients with IgLON5 autoimmunity, and describe the features helpful in distinguishing from amyotrophic lateral sclerosis (ALS).

Materials and methods

The Mayo Clinic Institutional Review Board (IRB) approved this study (IRB # 08-006647).

Serological testing

Specimens (serum and/or CSF) were evaluated by indirect immunofluorescence assay (IFA) on murine tissue composite as previously described. IgLON5-IgG specificity was confirmed by cell-based assay (CBA) on human embryonic kidney 293 cells that were transfected with an IgLON5 encoding plasmid (Euroimmun AG, Lubeck, Germany), as previously described [5]. Patients seropositive for IgLON5-IgG and sufficient serum volume were also tested for IgLON5-IgG subclass using subclass-specific secondary antibodies (mouse antihuman IgG1-4 Fc-specific FITC-conjugated [Southern Biotech]).

Clinical evaluation

IgLON5-IgG seropositive cases in the Mayo Clinic Neuroimmunology Laboratory database with available clinical data ($n = 32$) between 2003 and 2019 were reviewed to identify MND-like phenotypes. Ultimately, four cases with confirmed IgLON5 autoimmunity and an MND-like phenotype were identified. Of these four patients, two were clinically evaluated at Mayo Clinic, Rochester, one was clinically evaluated at Cleveland Clinic in Ohio, and one at the University Hospital of Geneva in Switzerland. Additionally, sera from 109 ALS patients evaluated at Mayo Neuromuscular clinic that met El-Escorial probable/definite criteria were tested for IgLON5-IgG by IFA and CBA.

Results

Four IgLON5-IgG seropositive patients with MND-like phenotype were identified (females, $n = 2$; median age 65.5 years [56–72 years]). All four patients demonstrated MND-like phenotype at the initial clinical presentation. Three patients met revised El-Escorial criteria for possible ALS and one for definite ALS. Presenting neurological symptoms included dyspnea with laryngospasm ($n = 3$) with one patient requiring tracheostomy due to vocal cord paresis, dysarthria ($n = 1$), choreiform movements ($n = 1$), and diplopia ($n = 1$). Two of the four patients had a history of rapid eye movement (REM) behavioral disorder (RBD). The pattern of weakness varied: upper-limb predominant ($n = 1$), lower-limb predominant ($n = 1$), bulbar predominant ($n = 1$), and generalized ($n = 1$). Only one patient reported cognitive/neuropsychiatric dysfunction with visual hallucinations and short-term memory loss as the disease progressed. None of the four cases had an underlying occult malignancy (three underwent whole body FDG-PET scans). MRI brain was performed in three patients (all except patient 3), which did not reveal any abnormality. The IgLON5–reactive IgG in two positive sera (patients 3 and 4) tested was of IgG4 subclass. None of the 109

probable/definite ALS cases experienced without laryngeal dysfunction, RBD or involuntary movement disorder; all were IgLON5-IgG negative.

Case reports (Table 1)

Case 1

A 65-year-old woman of East Indian origin presented with a 2-year history of intermittent dyspnea with episodic exacerbations and bilateral vocal cord paralysis. She also developed fasciculations and weakness predominantly in the upper limb and neck. The patient's family reported that she frequently enacted her dreams. As her intermittent dyspnea due to vocal cord paralysis continued to worsen, she underwent tracheostomy, and subsequently cordotomy and arytenoidectomy.

Neurological examination was significant for mild dysarthria, neck extensor weakness and bilateral asymmetric upper extremity weakness. She was hyperreflexic at the bilateral patellar tendons, and otherwise areflexic throughout. Sensory examination was normal, and no involuntary movements were detected.

Electrophysiologic testing demonstrated active denervation with chronic reinnervation involving distal and proximal myotomes of the cervical and lumbar segments. Although active denervation was not found in the thoracic segments, fasciculation potentials with changes of chronic denervation and varying motor units were noted. These findings were consistent with possible ALS as per revised El-Escorial criteria.

Serological evaluation of neural specific antibodies was remarkable for IgLON5-IgG. She was initiated on one-gram weekly intravenous methylprednisolone (IVMP) for 12 consecutive weeks and demonstrated clinical and electrodiagnostic stabilization at 3-month follow up.

Case 2

A 72-year-old gentleman with a 10-year history of intermittent choreiform movements limited to the left shoulder, progressed to diffuse involvement of all limbs. Two years prior to presentation, he began to experience dyspnea of insidious onset that progressed over a few months, leading to acute exacerbations requiring intubation on at least one occasion. Additionally, he endorsed 1-year of lower extremity weakness, short-term memory deficits, visual hallucinations, insomnia, dysarthria, dysphagia, and urinary urgency. Examination demonstrated mild dysarthria, slowed saccades, asymmetric mild lower limb weakness. DTRs were normal except for absent gastrocnemius reflex bilaterally. He had diffuse choreiform movements and a paraparetic gait. Family endorsed dream enactment behavior and a long-standing history of excessive day time sleepiness and snoring.

Electrophysiologic testing demonstrated active denervation with chronic partial reinnervation involving the left cervical and lumbosacral myotomes, characterized as possible ALS based on revised El-Escorial criteria. Polysomnography with audio/visual recording confirmed REM sleep without atonia (increased tonic muscle activity in the chin and excessive phasic axial and limb motor jerking during REM sleep), rapid periodic leg

movements of sleep, along with obstructive sleep apnea. Serological work up was positive for IgLON5 autoantibodies in serum and cerebrospinal fluid (CSF). CSF analysis was also notable for an elevated protein of 149 mg/dl but no pleocytosis or oligoclonal bands.

Six-weeks into the 12-week regimen of one-gram weekly IVMP, he reported significant improvement with his limb strength, balance, short-term memory, choreiform movements, bulbar symptoms, and urinary urgency. On completion of the aforementioned regimen, he was continued on IVMP 1 gram every other week for additional 8 weeks and started on mycophenolate mofetil.

At 6-month follow up, he reported complete resolution of neurological symptoms. However, he continued to experience obstructive sleep apnea (OSA) and infrequent dream enactment behaviors.

Case 3

A 66-year-old Caucasian woman presented with progressive history of weight loss, dysarthria, dyspnea on exertion, swallowing difficulty, emotional lability, diffuse asymmetric weakness (more prominent in the upper limbs), and urinary urgency.

Neurological examination was significant for tongue fasciculations, severe flaccid dysarthria, asymmetric lower facial weakness, diffuse muscle weakness, and atrophy which was more pronounced in the upper extremities, and diffuse hyperreflexia.

Electrodiagnostic testing performed 1.5 years after symptom onset demonstrated reduced recruitment of the motor units in the bilateral cervical myotomes, worse on the right, fasciculation potentials limited to the lower limbs and a superimposed length dependent sensorimotor peripheral neuropathy. Repeat electrodiagnostic testing, 4 months later demonstrated diffuse disorder of motor neurons involving the bulbar, cervical and lumbar myotomes consistent with definite ALS as per the revised El-Escorial criteria. Serum neural specific autoantibody evaluation 3 years after symptom onset was positive for IgLON5-IgG (CSF was not evaluated) but the patient died in her sleep before immunotherapy was initiated.

Case 4

A 53-year-old Caucasian man presented with a 1-year history of progressive diplopia, gait imbalance and fasciculations of the arms and legs. On presentation, his exam was notable for bilateral abducens palsy, diffuse spasticity, and hyperreflexia, dysmetria in the upper greater than lower extremities and a positive Romberg sign. Initial work up for myasthenia gravis included single fiber EMG of orbicularis oculi, as well as acetylcholine receptor and muscle-specific kinase antibodies which were negative. EMG revealed fasciculations in the upper and lower limb muscles. CSF evaluation showed normal protein and glucose and revealed a mild lymphocyte-predominant pleocytosis (nucleated cell count 11/mm^3) with normal protein and glucose, and an elevated IgG Index (0.73) and positive oligoclonal bands. Over the next 4 years he developed bilateral ptosis, dysarthria, neck weakness, and dysphagia. Fasciculations had spread to involve the tongue in addition to the extremities. He also demonstrated repetitive myoclonic jerks of the bilateral upper extremities, and

a gait disorder with lateral flexion of the trunk while standing or walking. Serum was tested 4 years from symptom onset and revealed IgLON5-IgG seropositivity (CSF was not evaluated).

Clinically, motor neuron involvement was present in the bulbar, and lumbar regions consistent with clinically possible ALS by revised El-Escorial criteria. EMG revealed an active denervation on chronic reinnervation involving the cervical and lumbar regions suggestive of a disorder of motor neurons. Polysomnogram revealed obstructive sleep apnea as well as sleep related hypoventilation. He was initiated on pulse dose IVMP 1 gram per week for 6 weeks, and later IVIG once per month for 6 months, without clinical improvement. He received mycophenolate mofetil, followed by rituximab (every 6 months for 1 year) with minimal clinical response. The patient died of a cardiac arrest 7 years after his initial presentation.

Discussion

Our observations in the current study support findings from prior reports of MND-like phenotype as either an initial presentation of IgLON5 autoimmunity, or developed as the predominant disorder in the illness course [6, 7]. While bulbar symptoms are frequently present with MND, additional features including recurrent acute episodic respiratory disturbance necessitating intubation/tracheostomy with or without stridor, vocal cord paresis, involuntary limb movements, sleep disorders beyond OSA (such as RBD, rapid PLMS), cognitive dysfunction, and dysautonomia were all clues to IgLON5 autoimmunity rather than classical ALS as diagnosis. Our patients all demonstrated limb and bulbar weakness, fasciculations, and EMG evidence for diffuse lower motor neuron disease. We also tested sera from 109 probable/definite ALS patients for IgLON5-IgG antibodies and all were negative. Of note none of these patients had parasomnias or involuntary movements or vocal cord dysfunction, which were often encountered in our IgLON5-IgG positive cases.

Similar to our study, age at diagnosis among patients with MND-related IgLON5 autoimmunity reported in prior studies ranged between 50 and 80 years (Table 2) [6, 7, 9]. While all previously reported patients were males, two of our four patients were females.

While a variety of treatment regimens were used across studies, IVMP was the most common followed by PLEX. Three of our four patients in our study received pulse weekly IVMP and one of them had significant improvement of choreiform movement, urinary urgency, cognition, motor strength, and balance. Our second patient who received treatment, demonstrated stabilization of clinical syndrome. The last patient (patient #4) had refractory disease, unresponsive to both first- and second-line agents. Prior studies have noted slight clinical benefit (with improvement pertaining to swallowing and respiratory issues) or stabilization [6, 7]. Refractoriness to the immunotherapies is not uncommon among IgLON5-IgG seropositive cases [5, 10]. Therefore, lack of favorable response to immunotherapy in two of three patients treated does not preclude IgLON5 neurological autoimmunity.

Neuropathological autopsy studies performed on brain and spinal cord specimens of IgLON5-IgG seropositive patients has identified deposition of hyperphosphorylated tau without inflammatory infiltrates across various structures including the anterior horn cell [8]. Notably, however, anterior horn cell involvement was milder in degree as compared to other brain regions, especially the brainstem tegmentum. Brain histopathological assessment of one IgLON5-IgG seropositive patient who died 2 years after symptom onset demonstrated perivascular CD8+ T-cell infiltrates in the posterior hypothalamus, amygdala, and brainstem with microglial activation, without any evidence of the brainstem tauopathy [11]. These findings suggest that the pTau deposition may be a late or secondary event following an initial immune-mediated disease process. Furthermore, primary cell cultures of rat hippocampal neurons treated with sera from anti-IgLON5-IgG patients demonstrated disorganization of the cytoskeleton, thus providing a link between antibody-mediated autoimmunity and neurodegeneration [1].

Our current series is limited by its retrospective design. Additionally, various immunosuppressive regimens in different permutations and combinations were used among the reported cases which limits comparison.

Conclusions

We report four IgLON5-IgG seropositive cases with MND-like phenotype and suggest that testing for IgLON5 antibodies should be considered among MND patients with additional clinical manifestations such as vocal cord paresis, parasomnias or involuntary movements at presentation. Recognition and treatment of this autoimmune disease with immunosuppressive agents may bring about significant neurological improvement in a minority of cases.

Abbreviations

ALS	Amyotrophic lateral sclerosis
ED	Erectile dysfunction
EDS	Excessive day time sleepiness
IVIG	Intravenous immune globulin
IVMP	Intravenous methyl prednisolone
OSA	Obstructive sleep apnea
PEG	Percutaneous endoscopic gastrostomy
PLEX	Plasma exchange
PLMS	Periodic limb movements of sleep
RBD	Rapid eye movement behavioral disturbance
REM	Rapid eye movement

References

1. Landa J et al. (2020) Effects of IgLON5 antibodies on neuronal cytoskeleton: a link between autoimmunity and neurodegeneration. Ann Neurol 88(5):1023–1027 [PubMed: 32740999]
2. Sabater L et al. (2014) A novel non-rapid-eye movement and rapideye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol 13(6):575–586 [PubMed: 24703753]
3. Gaig C, Compta Y (2019) Neurological profiles beyond the sleep disorder in patients with anti-IgLON5 disease. Curr Opin Neurol 32(3):493–499 [PubMed: 30694925]
4. Wenninger S (2017) Expanding the clinical spectrum of IgLON5-syndrome. J Neuromuscul Dis 4(4):337–339 [PubMed: 29103046]
5. Honorat JA et al. (2017) IgLON5 antibody: neurological accompaniments and outcomes in 20 patients. Neurol-Neuroimmunol Neuroinflamm 4(5):e385 [PubMed: 28761904]
6. Tao QQ et al. (2018) Motor neuron disease-like phenotype associated with anti-IgLON5 disease. CNS Neurosci Ther 24(12):1305 [PubMed: 30105827]
7. Werner J et al. (2021) Anti-IgLON5 disease: a new bulbar-onset motor neuron mimic syndrome. Neurology-Neuroimmunol Neuroinflamm 8(2):e692
8. Gelpi E et al. (2016) Neuropathological criteria of anti-IgLON5-related tauopathy. Acta Neuropathol 132(4):531–543 [PubMed: 27358064]
9. Videnovic A et al. (2022) Case 1–2022: a 67-year-old man with motor neuron disease and odd behaviors during sleep. N Engl J Med 386(2):173–180 [PubMed: 35020988]
10. Graus F, Santamaria J (2017) Understanding anti-IgLON5 disease. Neurol Neuroimmunol Neuroinflamm 4(5):e393 [PubMed: 28852690]
11. Erro ME et al. (2020) Anti-IGLON5 disease: A new case without neuropathologic evidence of brainstem tauopathy. Neurol-Neuroimmunol Neuroinflamm 7(2):e651 [PubMed: 31826985]

Table 1

Summary of cases from the current study

Case	Age at diagnosis(years)/ Gender	Initial symptoms	Symptoms suggestive of IgLON5 autoimmunity	Time from symptom onset to diagnosis	Treatment regimen	Treatment outcome
1	65/female	Episodic dyspnea, bilateral vocal cord paralysis	Recurrent episodic dyspnea necessitating tracheostomy, RBD, bilateral vocal cord paralysis	2 years	Weekly IVMP for 12 consecutive weeks, once	Stabilization of motor symptoms
2	72/male	Intermittent choreiform movements, episodic dyspnea	Recurrent episodic dyspnea necessitating intubation at least on one occasion, involuntary movements, sleep disturbance (RBD, rapid PLMS)	10 years of choreiform movements and 2 years of bulbar symptoms	Weekly IVMP for 12 consecutive weeks, twice followed by 1000 mg BID of mycophenolate mofetil	Improvement of choreiform movements, RBD, urinary urgency, cognition, and gait instability
3	66/female	Bulbar symptoms	Vocal cord paralysis	3 years	None	Died in her sleep
4	56/male	Ophthalmoplegia, gait imbalance, fasciculations	Sleep disturbance (OSA), gait imbalance, head drop	4 years	Weekly IVMP for 6 weeks, monthly IVIG for 6 months, Mycophenolate mofetil for 3 months, Rituximab every 6 months × 1 year	

IVMP intra venous methyl prednisolone, *RBD* rapid eye movement behavioral disturbance, *PLMD* periodic limb movement disorder

Table 2

Summary of prior reported cases of motor-neuron-disease-like manifestation with IgLON5 disease

Study (number of cases)	Age at diagnosis/sex	Initial symptom	Symptoms suggestive of IgLON5 autoimmunity	Time from symptom onset to diagnosis	Treatment regimen	Treatment outcome
Videnovic et al. (2022) [9]	67/male	Postural instability, falls, dysarthria, dysphagia, and clumsiness of hands	Sleep disturbances (RBD, EDS, OSA), bulbar issues (dysarthria, dysphagia, hypophonia), gait instability, cognitive disturbance, urinary urgency and frequency	3.5 years	Riluzole, IVMP 1 g/day × 5 days, IVIG 2 g/kg per month × 2 followed by Rituximab 1 gm × 2 given 2 weeks apart	Improvement of RBD and EDS
Werner et al. (2021) [7]	74/male	OSA	Recurrent episodic dyspnea necessitating tracheostomy, sleep disturbance (PLMD, NREM parasomnia), bilateral vocal cord paresis, stridor, dysautonomia	2 years	Mercaptopurine 75 mg/day PO	Improvement of dysphagia resulting in PEG removal
	52/male	Dysphagia	Recurrent episodes of dyspnea with stridor with recommendation for tracheostomy, RBD	3.5 years	IVMP 1 g/day × 5 days, alternate day PLEX, Rituximab 375 mg/m^2, once)	Stable at 6 months
	77/male	Dysarthria	Recurrent episodic dyspnea necessitating tracheostomy, bilateral vocal cord paresis, dysautonomia	2 years	PLEX, monthly IVIG (0.4 g/kg for 5 days), twice; rituximab (375 mg/m^2, twice)	Partial improvement with dysphagia
	63/male	Episodic dyspnea, OSA, parasomnia	Recurrent episodic dyspnea necessitating tracheostomy, sleep issues (PLMD, RBD, REM parasomnia), bilateral vocal cord paresis, recurrent depression, cognitive disturbance (reduced impulse control and semantic fluency), dysautonomia (ED, palpitations, signs of BPH)	1.5 years	IVMP 1 g/day × 5 days, twice; PLEX, rituximab (375 mg/m^2, once)	Stable, persistent symptoms without deterioration
	70/male	OSA	Recurrent episodic dyspnea necessitating tracheostomy, sleep issues (RBD, OSA, PLMD, REM motor activity), bilateral vocal cord paresis, dysautonomia (hyperhidrosis)	7 months	IVMP 1 g/day X5 days, PLEX, rituximab 375 mg/m^2, once	Stable, persistent symptoms without deterioration
Tao et al. (2018) [6]	57/male	Dysphagia	Recurrent respiratory issues necessitating intubation, involuntary movements, sleep abnormalities (snoring), cognitive issues (abnormal behavior and consciousness)	2 years	IVMP 1 g/day × 3, 500 mg/day × 3, oral prednisone; IVIG 0.4 g/kg × 5	Initial transient improvement followed by disease progression

ED erectile dysfunction, *EDS* excessive day time sleep, *IVIG* intravenous immuno-globulin, *IVMP* intravenous methyl prednisolone, *OSA* obstructive sleep apnea, *PEG* percutaneous endoscopic gastrostomy, *PLEX* plasma exchange, *PLMS* periodic limb movements of sleep, *RBD* rapid eye movement behavioral disturbance, *REM* rapid eye movement