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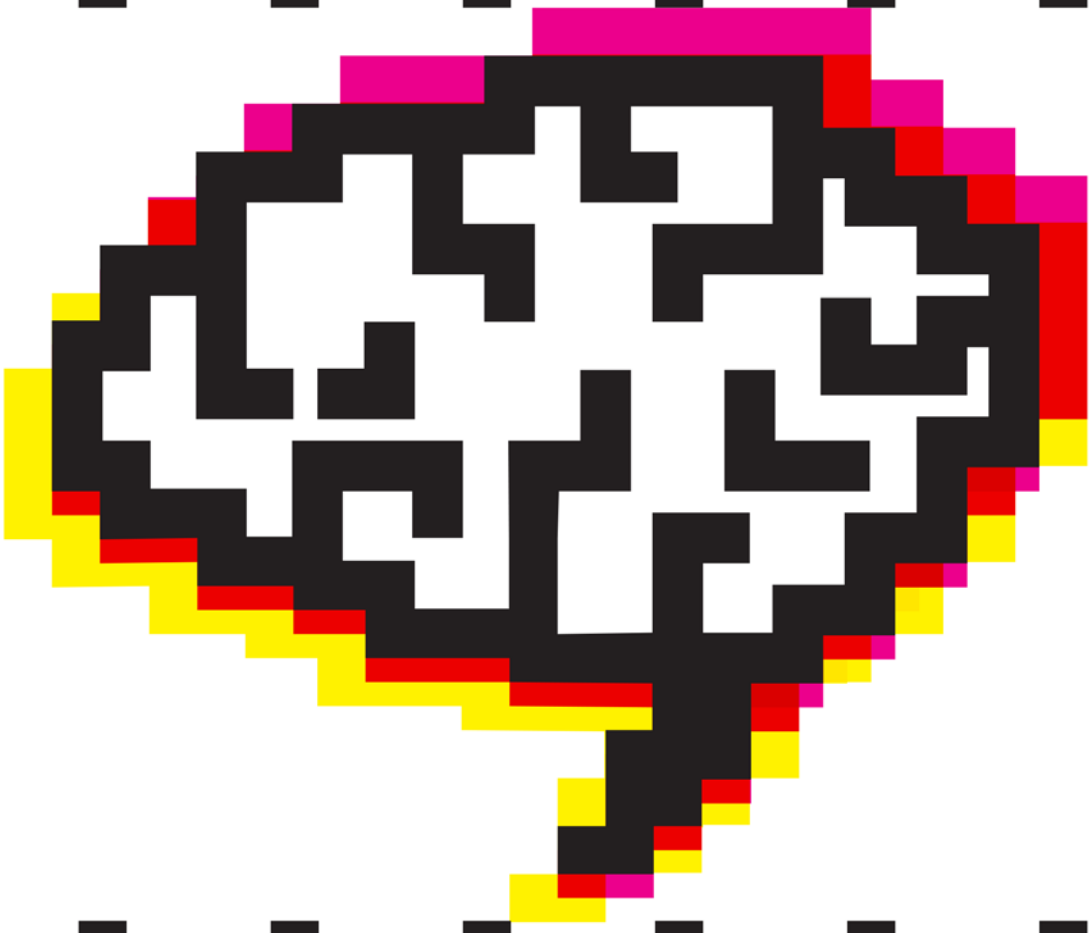

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Review

Diana Karla García-Nuño,[1] Luis Hayram de Jesús Ramírez Vega,[1] José Alberto Soto Escageda,[1] Carlos Zúñiga Ramírez.[1]

[1]Movement Disorders and Neurodegenerative Diseases Unit, "Fray Antonio Alcalde" Civil Hospital of Guadalajara.

Anti-IgLON5-Related Tauopathy

Taupatía asociada a anticuerpos anti-IgLON5

Abstract

Antibodies against IgLON5 have been found in subjects who develop sleep disorders with gait instability, abnormal ocular movements, bulbar symptoms, movement disorders, dysautonomia and cognitive decline. These patients share the HLA DRB1*1001 and DqB1*0501 alleles and hystopathological features of neurodegeneration with neuronal hyperphosphorylated Tau deposits mostly in hypothalamus and brainstem without inflammatory changes. Even though antibody-associated neurological diseases usually improve after immunotherapy, this entity shows poor response and a fatal prognosis, representing a mixture of immunological and neurodegenerative mechanisms.

Keywords

Neurodegeneration, IgLON5, tauopathy, sleep disorders, parasomnia, autoantibodies.

Resumen

Los anticuerpos contra IgLON5 se han encontraron en sujetos con un cuadro caracterizado por alteraciones del sueño acompañadas de inestabilidad para la marcha y alteración de movimientos oculares, síntomas bulbares, movimientos anormales, disautonomía y deterioro cognitivo. Estos pacientes poseen alelos HLA DRB1*1001 y DQB1*0501 y hallazgos histopatológicos de neurodegeneración con acúmulo intracelular de proteína Tau hiperfosforilada sobre todo en hipotálamo y tallo cerebral, sin cambios inflamatorios. Aunque las enfermedades neurológicas asociadas a anticuerpos contra antígenos de superficie suelen responder bien a la inmunoterapia, en esta enfermedad muestran pobre respuesta y un pronóstico generalmente fatal, por lo que representa un cruce entre los mecanismos inmunológicos y de neurodegeneración.

Palabras clave

Neurodegeneración, IgLON5, taupatía, trastornos del sueño, autoanticuerpos.

Introduction

In 2014, Sabater *et al.*[1] reported a group of eight subjects who presented a picture characterized by parasomnias present in both rapid eye movement (REM) and non-rapid eye movement (NREM) sleep, obstructive sleep apnea, central hypoventilation, and a syndrome similar to Progressive Supranuclear Palsy (PSP) with an unfavorable prognosis. All the analyzed subjects presented anti-IgLON5 antibodies, a neuronal surface protein, in addition to sharing the haplotype HLA-DRB1*1001 and HLA-DQB1*0501. The neuropathological analysis found a neurodegenerative process, the presence of phosphorylated tau (p-Tau) protein, and neuronal loss, corresponding to an entity that had not been described until then. In less than four years since its publication, more cases have been reported in different parts of the world with similar characteristics and it has been named based on its clinical and pathological characteristics as IgLON5 encephalopathy,[2] Parasomnia with anti-IgLON5 antibodies,[3] Anti-IgLON5-related tauopathy,[4] Anti-IgLON5 syndrome,[5] and Anti-IgLON5 disease.[6]

The autoimmune-related neurological diseases are very heterogeneous entities in which antibodies against different components of nerve cells are found and usually produce an acute clinical picture,[7] whereas neurodegenerative diseases generally have a slow and insidious evolution. Immunological mechanisms have been proposed to explain the origin of neurodegenerative diseases, although the role of antibodies in these processes is not entirely clear.[8] To know this new pathology that contains characteristics of both could help better understand the way in which the neurodegenerative process is related to the immunological mechanisms of various entities.
The objective of this article is to offer an updated review of the literature on this entity since it represents a diagnostic and therapeutic challenge for the clinician, and its early recognition could lead to a better prognosis for the affected subjects by establishing an opportune management.

Epidemiology

Fifty-one subjects with anti-IgLON5 antibodies have been reported in different countries of Europe (22 cases), as well as the United States (26 cases), Brazil, Australia, and China (1 case in each). Twenty-seven of these (53%) were women, so the presentation shows no clear preference for gender. Clinical information for 45 out of the 51 subjects is available. (Table 1) It can be observed that the onset of the disease occurs around 63 years, with appearances ranging between 46 and 83 years. The duration of the disease ranges from two months to 19 years, with an average of 32 months between onset of symptoms and fatal outcome, usually with a poor response to immunomodulatory treatments and a gloomy prognosis.[1,6,9]

Pathophysiology

Neuronal antibodies are classified according to the location of the antigen against which they are directed: surface antigens (involved in synaptic transmission, plasticity, and neuronal excitability) such as anti-NMDA receptor encephalitis, whose course of disease is associated with antibody titers and presents good response to immunotherapy; or intracellular antigens such as encephalitis by anti-Hu, anti-Yo, and anti-Ri antibodies, whose course of disease does not correlate with antibody titers, and presents poor response to treatment.[10,11] In this disease's case, antibodies have been found

Corresponding author:
Dr. Carlos Zúñiga-Ramírez.
Av. Rubén Darío 1208 piso 2 interior 1, Col. Italia Providencia.
Guadalajara, Jalisco; México. C.P. 44648
e-mail: c.zuniga.ramirez@gmail.com

Table 1. Clinical and polysomnographic profile of subjects diagnosed with IgLON5 tauopathy.

Report (number of cases)	Sex (M/F)	Age of onset in years (mean, range)	Duration (mean, range)	Parasomnias	Sleep Apnea
Sabater, 2014. España (6), Alemania (1), Italia (1)	3/5	59, 52 to 76	4.5 years, 2 to 144 months	8/8	8/8
Bahtz, 2014. Alemania (2)	1/1	71 and 62	4 and 1 years	N/A	N/A
Hôgl, 2015. Austria (1)	Female	53	13.5 years	+	+
Simaburuko, 2015. Brasil (1)	Female	65	6 years	+	+
Montojo, 2015. España (1)	Female	62	8 years	N/A	N/A
Brûgemann, 2016. Alemania (1)	Male	62	2 years	+	+
Haitao, 2016. China (1)	Female	63	1 year	+	+
Gelpi, 2016. Inglaterra (1)	Male	48	12 years	+	N/A
Schrôder, 2017. Alemania (1)	Female	75	2 years	+	-**
Gaig, 2017. Europa (7), Australia (1)	4/4	64, 46 to 83	2.8 years, 2 to 228 months	6/8	8/8
Honorat, 2017. EEUU (20)*	9/11	62, 46 to 75	2.5 years, 2 to 156 months	3/20	11/20
Total (45)	25/21	63, 46 to 83	32 months	23/42	31/41

*The clinical information of only 20 subjects of the 26 in this study is available.
**The polysomnography was performed with the patient under mechanical assisted ventilation.

directed against the IgLON5 molecule. The function of IgLON5 is not entirely clear, but it is known that the IgLON family consists of cell adhesion molecules (CAM) of the immunoglobulin superfamily[12] that bind to the neuronal plasma membrane by a glycosylphosphatidylinositol (GPI) anchor and are important for the process of synapse formation, neuronal development, synaptic plasticity, and learning.[13] This molecule is distributed mainly on the surface of brain cells, although it is also found in the intestine and kidney, and apparently is important for the formation of axonal trajectories and production of synapses during neurodevelopment.[9,12] Antibodies of the IgG type against IgLON5 have been found in its four subclasses in the serum of the affected subjects, predominantly IgG1 and IgG4.[5,9] Of the 45 cases with this pathology in which the IgG subtypes were analyzed, IgG1 antibodies were found in 44 subjects and IgG4 antibodies in 42 of them.[6,9] Although subtype Ig4 antibodies are usually more abundant than Ig1 (ratio 2:1), both seem to have a preponderant role in the development of this disease.[5]

It was described that anti-IgLON5 antibodies of IgG1 subclass produce an internalization of IgLON5 that does not revert when eliminating the antibodies, but this effect is not produced by IgG4 antibodies.[5] In other diseases mediated by antibodies such as anti-NMDAR encephalitis, this same internalization effect of the antigen has been found in the presence of the antibody, but the loss of NMDAR is reversible by eliminating the antibodies.[14] This difference between the two diseases may explain the poor response to immunotherapy seen in anti-IgLON5 tauopathy, although it is believed that in early stages of the pathological process it could be partially responsive to treatment.[10]

It is accepted that antibodies of Ig4 subclass have an immunoregulatory function in allergic processes, so that the change of IgG1/IgE to IgG4 produces inhibition of the inflammatory response with improvement of allergic symptoms, therefore its role in the pathophysiology of this illness is unclear.[3] It is believed that IgG4 antibodies act

Laryngeal Stridor	Hypersomnia	Apnea-Hypopnea Index	O_2Sat Nadir	HLA DQB1*0501 or DRB1*1001	Improvement with immunotherapy
6/6	5/8	20-84	75-88%	4/4	1/8
N/A	1/2	N/A	N/A	N/A	1/2
+	+	14.6	66%	+	-
+	+	43	N/A	+	-
+	N/A	N/A	N/A	N/A	N/A
-	-	61	86	+	+
-	+	17.5	72	+ (DQB1)	+
N/A	+	N/A	N/A	N/A	-
+	-	0.9**	91%**	N/A	+
0/8	5/8	N/A	N/A	6/8	0/8
1/20	N/A	N/A	N/A	N/A	7/9
11/40	15/43			14/16	12/33

by interfering with the normal protein-protein interactions of the target antigen, altering the stability of cell adhesion.[3]

It has been proposed that the presence of these antibodies may be secondary to a primary neurodegenerative process, playing a less important role in the pathophysiology of this disease. This theory is supported by the fact that the picture tends to progress even when the concentration of antibodies decreases in response to treatment, as well as by the chronic course that has been found in some subjects, and the p-Tau protein aggregates in the absence of inflammatory processes in the subjects studied.[1,4] On the other hand, the majority of those affected by this disease have the HLA alleles DRB1*1001 and HLA DQB1*0501 that are associated with greater susceptibility to autoimmune diseases. The anti-IgLON5 antibodies do interact with the antigen and produce specific effects (internalization and alteration of its adhesion function) so it is believed that the IgLON5 dysfunction induced by antibodies can interfere with the interaction of this protein with the cytoskeleton and destabilize the neuronal microtubule system, induce hyperphosphorylation and accumulation of microtubules associated with tau protein, leading to neuronal dysfunction and subsequent neurodegeneration.[4]

Histopathology

The main histopathological findings consist of the symmetric subcortical cluster of 3-repeat and 4-repeat (3R and 4R) tau isoforms, exclusively intracellular, in the form of neurofibrillary tangles (NFT), pre-NFT and neuropil strands, mainly in the hypothalamus and the brainstem tegmentum.[1] Tauopathy data has been found also from the neocortex, the hippocampus (accentuated in CA2), and the basal ganglia to the cerebellum and posterior horns of the cervical spine, showing a rostrocaudal gradient of severity.[4] There is neuronal loss with astrogliosis and variable intensity

microglial activation in the thalamus, hypothalamus, periaqueductal gray matter, pontine tegmentum, mesencephalic tegmentum, reticular formation, magnocellular nucleus, and nucleus ambiguus.[1] This neuronal loss correlates with the presence of NFT, without finding deposits of β-amyloid, α-synuclein, IgG4, or tau pathology data in astrocytes or oligodendrocytes.[1] In one subject, TDP-43 histopathology was found in the microglia, thalami, striatum, brainstem, hippocampus, and nucleus basalis of Meynert.[15] The dysfunction of the affected diencephalic structures and brainstem is related to manifestations such as sleep disorders, gait instability, bulbar symptoms, and dysautonomia.[4]

Clinical manifestations

It is a late-onset condition, usually seen from the sixth decade of life, with a subacute presentation that can last from two months to several years.[6] The symptoms occur with variable severity and can appear in different combinations and periods of time, giving rise to different clinical subtypes of the disease, among which four presentations predominate:

(1) A sleep disorder with parasomnia and respiratory distress.
(2) A bulbar syndrome.
(3) Syndrome similar to PSP.
(4) Cognitive impairment with or without chorea.[6]

A sleep disorder is the characteristic syndrome of this disease—almost all subjects are affected to a greater or lesser degree. This is characterized by parasomnias or abnormal behaviors during sleep such as movements or shaking of the extremities, vocalizations, lip suction, gestures, and ventilatory phenomena such as stridor, snoring, periods of apnea, among others. It is very common for the affected individuals to be presented by a severe insomnia of several years of evolution, which generates fatigue and severe daytime sleepiness.[15,16]

Of the 45 subjects whose clinical information is reported in the literature, 34 presented bulbar symptoms such as dysphagia, episodic dysarthria, diurnal stridor, dyspnea, and vocal cord paralysis.[17,18] (Table 2) These can be complicated by aspiration pneumonia, central hypoventilation with respiratory failure and respiratory acidosis.[15,16]

It can present with supranuclear gaze palsy and other oculomotor abnormalities (i.e. saccadic intrusions, nystagmus, horizontal gaze palsy, vertical gaze palsy, hypometric saccades), which have been seen in 44% of those affected.[1,4,9,18] These subjects usually show significant gait instability and imbalance due to parkinsonism, rigidity and dystonia of the lower limbs or ataxia, which causes frequent falls and ends in confinement to a wheelchair.[1,19,20] Gait abnormality has been severe in half of the subjects reported, accompanied by imbalance, falls, and abnormal postural reflexes that suggest more a degeneration of subcortical origin.[21] The presentation of supranuclear gaze palsy with postural alterations forces us to think about a syndrome-like presentation similar to PSP.[6]

Cognitive impairment occurred in 37% of the subjects reported, one of them with severe dementia.[20] Those who received a neuropsychological evaluation showed alterations in attention, executive functions, episodic memory, processing speed, visuospatial functions, and apraxia[1,2,19,22] suggesting subcortical impairment. Cognitive impairment may or may not be accompanied by abnormal movements such as chorea,[2,22] orofacial, cervical, and limb dystonia,1 myoclonus,[9,20] parkinsonism with bradykinesia, camptocormia, pleurothotonus, gait drag, tremor, and hypomimia.[19,22] A subject debuted as stiff person syndrome.[9]

In half of the cases there were findings of autonomic dysfunction such as urinary urgency, incontinence, enuresis, hyperhidrosis, sialorrhea, orthostatic hypotension, tachycardia and bradycardia accompanied by syncope and sudden death[1,4,19] and a case with Takotsubo cardiomyopathy.[18]

Some subjects have also shown neuropsychiatric manifestations such as depression,[2,20] hallucinations, delirium,[9,20] anxiety, obsessive thoughts, and compulsions.[15] In addition, two cases with palpebral ptosis and one with peripheral facial palsy have been reported.[16,17]

Diagnosis

Based on the similarities of the reported cases, Gelpi *et al*.[4] propose diagnostic criteria for anti-IgLON5-related tauopathy with three levels of probability: definitive, probable, and possible. This is based on the findings of neuropathological studies, the presence of anti-IgLON5 antibodies in serum and cerebrospinal fluid (CSF), clinical characteristics, and the presence of associated HLA alleles.4 (Table 3)

Polysomnography is considered one of the main diagnostic tools to perform, because sleep disorders are part of the cardinal features of this disorder. Almost all reported subjects had sleep disorders. Findings include decreased total sleep time and sleep efficiency, complex parasomnia with abnormal behaviors more frequent at the beginning of the night, rapid leg movements during wakefulness and after the beginning of sleep, presence of vocalizations, gestures, repetitive stereotyped movements of upper limbs and directed behaviors in stage N2, REM sleep behavior disorder, stridor, and obstructive sleep apnea.[1,6] (Table 1) In one subject, nocturnal epilepsy of the frontal lobe was found.[9]

The search for anti-IgLON5 antibodies can be performed with samples of serum and CSF, either from live subjects or from previous samples of deceased subjects.[4] The specificity of the antibody for the diagnosis of this disease is very high. In a study with 298 controls of different neurological pathologies, only one presented positivity in serum (but not in CSF) for anti-IgLON5 antibodies. This 81-year-old subject presented a PSP picture of more than 20 years of evolution without sleep disorders and negative for HLA DRB1*1001 and DQB1*0501.[1,23] Out of 22 subjects reported by Gaig *et al*. with analysis of anti-IgLON5 antibodies, all had a positive result in serum and two negative in CSF (both with a syndrome similar to PSP), so the sensitivity is higher in serum samples.[6] The majority of cases in which antibodies against other neuronal antigens have been searched (NMDAR, GABABR, AMPAR, mGluR1, mGluR5, DPPX, LGI1, Caspr2, AChR, MuSK, titin, gangliosides) have been negative,[1,17,22] except one case in which they coexisted with anti-GAD65 antibodies and in another case with anti-LGI1.[9]

The typing of HLA genes consists of determining which of all known variants for a locus are present in an individual. In the particular case of IgLON5 disorder, it is important to carry out the typing, since it was found that the risk ratio of HLA-DRB1*1001 is 36 times more frequent in subjects who develop the anti-IgLON5 disorder than in the general population, while that of HLA-DQB1*0501 is 3.5 times more frequent.[6] Of the 16 cases in which typing was performed, 13 had both alleles present and in one case it was positive for DQB1*0501 and negative for DRB1*1001. (Table 1) Keep in mind that the HLA allele can be typed in post-mortem analysis of DNA samples.[4]

In most subjects the MRI study is reported as normal. From a group of 22 subjects, Gaig *et al*. found three had mild atrophy in the brainstem and cerebellum, and one had bilateral hippocampal atrophy.[6] Ten of 20 subjects reported by Honorat *et al*. had nonspecific findings (six with leukoaraiosis, six with mild-moderate cerebral atrophy, and two with cerebellar atrophy—both with ataxia)[9] while a hummingbird sign and midbrain atrophy were found in a subject with a PSP-like syndrome.[18]

PET/CT scans are not considered a routine study. Its performance was reported in only one case in which hypermetabolism was observed in the primary sensorimotor cortex, basal ganglia, and cerebellum as well as hypometabolism in other areas of the cerebral cortex. These findings reversed after treatment, so it could serve as a prognostic indicator of the disease.[24]

It is important to carry out complementary tests to rule out other diagnoses that explain the symptoms of this disorder. The CSF analysis showed a slight decrease in the serum glucose/CSF ratio and an increase in protein concentration, adequate levels of hypocretin, and other normal parameters.[1,17,22] Studies such as electroencephalogram and electromyography are reported as normal in all affected subjects.[1,6]

Table 2. Neurological manifestations reported in subjects diagnosed with IgLON5 tauopathy.

Report (number of cases)	Gait instability	Parkinsonism	Chorea	Ataxia	Alterations of eye movement
Sabater, 2014. (8)	5/8	0/8	4/8	3/8	5/8
Bahtz, 2014. (2)	2/2	0/2	0/2	1/2	0/2
Hôgl, 2015. (1)	+	-	-	-	-
Simaburuko, 2015. (1)	+	-	+	+	-
Montojo, 2015. (1)	+	-	-	-	+
Brûgemann, 2016. (1)	+	+	-	-	+
Haitao, 2016. (1)	+	+	+	+	-
Gelpi, 2016. (1)	+	-	+	+	+
Schrôder, 2016. (1)	-	-	-	-	-
Gaig, 2017. (8)	6/8	4/8	1/8	N/A	5/8
Honorat, 2017. (20)	14/20	5/20	2/20	5/20	7/20
Total (45)	33/45 (73%)	11/45 (24%)	10/45 (22%)	12/37 (32%)	20/45 (44%)

Table 3. Neuropathological criteria to define the tauopathy underlying the anti-IgLON5 syndrome. Extracted from Gelpi, 2016.

Posible	All the following requirements: -Neurodegenerative features with neuronal loss and gliosis in areas of the brain demonstrating hyperphosphorylated tau pathology without the presence of an inflammatory infiltrate. -Selective neuronal involvement from deposits of pTau forming neurofibrillary tangles, pretangles and neuropil threads with both 3R and 4R tau isoforms in the inclusions. -Tau pathology predominantly affects subcortical structures including hypothalamus, brainstem tegmentum, and upper spinal cord.
Probable	Criteria for possible and at least one of the following: -Clinical history suggestive of a disorder of sleep (parasomnia during REM and non-REM sleep with sleep apnea) or of the brainstem, mainly with bulbar dysfunction (dysarthria, dysphagia, stridor, central hypoventilation). -Presence of alleles HLA-DRB1*1001 and HLA-DQB1*0501
Definitivo	Criteria for possible and the presence of anti-IgLON5 antibodies in serum or CSF.

Treatment

Therapy directed against anti-IgLON5 antibodies remains ineffective. The vast majority of subjects do not respond to immunotherapy, unlike other autoimmune encephalitis. Although at the end of the treatment the antibody titers in the CSF decrease, this is not related to a clinical improvement in the affected subjects.[1] Despite this, most of the neurological syndromes associated with antibodies against cell surface proteins respond to immunotherapy, so it is reasonable to administer it even before conclusive evidence of treatment is available.[22]

Different immunomodulatory treatments have been administered: intravenous immunoglobulin (IVIG),

Bulbar signs	Dysautonomia	Cognitive impairment	Neuropsychiatric symptoms
8/8	7/8	2/8	1/8
2/2	0/2	1/2	2/2
+	-	-	-
-	-	+	+
+	+	-	-
-	+	+	-
-	-	+	-
+	+	-	-
+	-	-	-
8/8	4/8	5/8	N/A
12/20	9/20	6/20	6/20
34/45 (75%)	23/45 (51%)	17/45 (37%)	10/45 (22%)

plasmapheresis, cyclophosphamide, rituximab, glucocorticoids, and mycophenolate mofetil. There is no clear response to treatment to this date. In some cases the improvement is usually mild, mainly of the motor symptoms. (Table 1)

Only one of the eight original subjects reported by Sabater *et al*. had improvement with steroids, rituximab, and IVIG treatment, but he presented with sudden death a few days later with no determined cause of death.[1] One subject in China showed significant improvement with immunomodulatory treatment (IVIG and mycophenolate mofetil), in which the sleep disorder, involuntary movements, and gait disorder disappeared, the titers of anti-IgON5 antibodies in serum decreased to 1:32, and were negative in the CSF.[22] In the follow-up PET/CT scan two months later, the metabolic alterations found before treatment also decreased.[24] Another subject in Germany had symptoms improve after plasmapheresis and methylprednisolone IV, followed by prednisolone PO, but he died five weeks later after the stridor symptoms worsened.[17] In a series of 20 subjects positive for anti-IgLON5, 10 of them received some immunotherapy with favorable results (partial or complete sustained improvement) in seven of them.[9]

Symptomatic treatments for stridor and sleep apnea with BiPAP and CPAP have shown favorable but transient results.[2,16,19] Manifestations such as rigidity, bradykinesia, postural disorders, and dystonia have shown moderate or no response to levodopa, baclofen, trihexyphenidyl, and benzodiazepines, the same failure seen with antiepileptic drugs aimed at treating myoclonus,[19,20,22] although one case was reported that, when diagnosed as Huntington's disease, decreased abnormal movements with haloperidol.[2]

In case of presenting life-threatening complications such as central hypoventilation, respiratory failure associated with stridor, vocal cord paralysis and dysphagia it may be necessary to subject the patient to mechanical ventilation, tracheostomy, and gastrostomy.[1,16-18]

Prognosis

The tauopathy associated with anti-IgLON5 antibodies has a poor prognosis in the short and medium term.[1,6] Management with various immunomodulators shows some improvement in symptoms, but it doesn't prevail over time. Of all the

subjects reported only 12 presented improvement in the symptoms with immunomodulatory treatment (Table 1) but it did not improve the course of the disease. This speaks of the poor prognosis for the subjects who suffer from it, but there is no factor associated with a good or bad prognosis due to the heterogeneity of the course of the disease.

The clinical presentation in each subject will determine the degree of disability they will present, as well as the amount of risk of short-term mortality. For instance, it is more likely for a laryngeal stridor or vocal cord paralysis episode to rapidly culminate in death than it is for dementia or chorea pictures.[6,17,20]

Conclusions

The anti-IgLON5-related tauopathy shows variable presentations, some characteristics such as sleep disorders, accumulations of p-Tau, HLA alleles, and the presence of previously unknown antibodies. The suspicion of this disease will help accelerate an accurate diagnosis, which would make a difference in the treatment because it is suggested that it could be responsive to immunotherapy in its early stages—otherwise, the prognosis is bleak. Understanding the link between anti-IgLON5 antibodies and the accumulations of p-Tau can reveal what neurodegenerative diseases and immunological mechanisms have in common, in order to modify their management.

Conflicto de intereses
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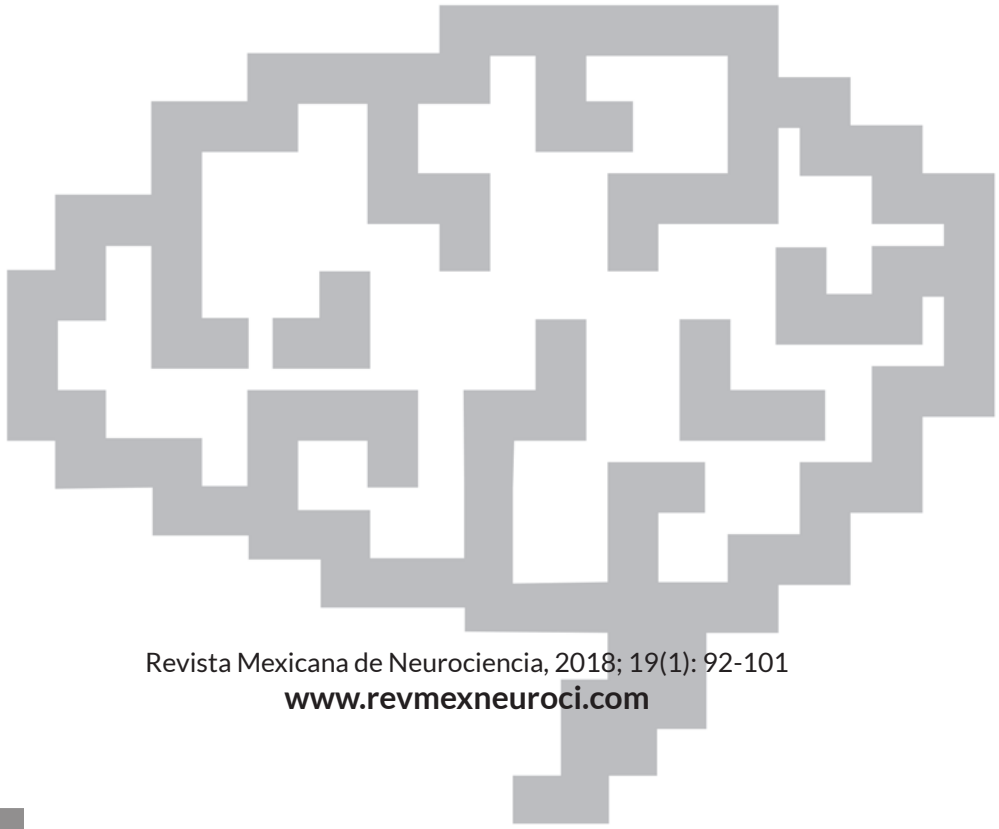

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