Mateus M. Simabukuro, MD
Lidia Sabater, PhD
Tarso Adoni, MD, PhD
Rubens Gisbert Cury, MD
Mônica Santoro Haddad, MD
Camila Hobi Moreira, MD
Luana Oliveira, MD
Mateus Boaventura, MD
Rosana Cardoso Alves, MD, PhD
Leticia Azevedo Soster, MD
Ricardo Nitrini, MD, PhD
Carles Gaig, MD
Joan Santamaria, MD
Josep Dalmau, MD, PhD
Francesc Graus, MD, PhD

Neurol Neuroimmunol Neuroinflamm
2015;2:e136; doi: 10.1212/NXI.0000000000000136

SLEEP DISORDER, CHOREA, AND DEMENTIA ASSOCIATED WITH IgLON5 ANTIBODIES

OPEN

A novel syndrome characterized by a distinctive sleep disorder accompanied by variable symptoms of brainstem involvement and a highly restricted haplotype was recently described in association with antibodies to a neuronal cell adhesion protein named IgLON5. Because of the symptoms and chronic disease progression, most of these patients are primarily seen by specialists in sleep and neurodegenerative disorders. Since the initial description of this encephalopathy in 2014, only 1 additional patient has been reported.[1] In order to improve clinical recognition we report a new patient who presented with the characteristic sleep dysfunction and subsequently developed chorea.

Case report. A 71-year-old right-handed woman was referred for evaluation of chorea. She had been well until 6 years earlier, when she presented with abnormal movements and behavior during sleep. These ranged from simple to complex movements (threading a needle, salting food, dabbing perfume) and were associated with vocalizations, "snoring," and excessive daytime sleepiness. A polysomnogram (PSG) without video recording detected obstructive sleep apnea (OSA). Treatment with continuous positive airway pressure mask was started, but the nocturnal abnormal movements and behaviors persisted. One year after symptom onset, she developed chorea, progressive memory loss, depression, and mild gait imbalance. An initial neurologic consultation suggested the diagnosis of Huntington chorea, and she was treated with haloperidol, which improved the abnormal movements. On neurologic examination she scored 20 points on the Mini-Mental State Examination. Neuropsychological testing showed impaired executive function (planning, verbal fluency), visuospatial function (clock drawing, Rey Complex Figure Test), and episodic memory (Wechsler Memory Scale-Revised and Rey Auditory Verbal Learning Test). She had restricted upward voluntary gaze and mildly ataxic gait; the chorea predominated in the head and face (video at Neurology.org/nn) and was accompanied by mild motor impersistence and hypotonia. The remainder of the neurologic examination was normal. Laryngoscopy showed no vocal cord paresis.

Brain MRI was normal and repeat CSF examinations showed mild pleocytosis (ranging from 5 to 9 cells per mm^3) and increased protein concentration (ranging from 56 to 62 mg/dL); oligoclonal bands were absent. Testing for antibodies against cell surface proteins showed IgG4 antibodies against IgLON5 in serum (titer 1:2,560) and CSF (1:64) using an immunofluorescence cell-based assay with human embryonic kidney cells expressing IgLON5, as reported.[2] The human leukocyte antigen (HLA) haplotype was HLA-DRB1*1001 and HLA-DQB1*0501. In a nocturnal video-PSG (under treatment with haloperidol), sleep efficiency was approximately 62% (normal > 75%). There were clear periods of normal N2 and N3 stages (50% of the total sleep time [TST]). REM stage was 8% of the TST, and there were abnormal limb and body jerks. The rest of the sleep (42% of TST) was characterized by diffuse theta activity without sleep spindles, K complexes, delta waves, or REMs. Occasionally during N2 sleep stage the patient had continuous simple limb and body movements. Episodes of OSA were frequent (apnea-hypopnea index: 43 per hour).

Since the diagnosis of IgLON5 encephalopathy the patient has been treated with IV immunoglobulin and rituximab; however, the symptoms remain unchanged.

Discussion. We report a case of IgLON5 sleep disorder associated with chorea and dementia. IgLON5 is the most recently identified antigen within the category of neurologic disorders associated with antibodies against cell surface or synaptic proteins and establishes a new syndrome.[2] This disorder was first described in 8 patients and differs substantially from previously described autoimmune encephalitis because patients often have a protracted clinical course, the distinctive feature is sleep dysfunction, the disorder is refractory to immunotherapy, and preliminary neuropathologic findings suggest a neurodegenerative process. All of the initial patients had a unique and novel sleep disorder characterized by non-REM and REM parasomnia with abnormal movements and OSA that differed from agrypnia excitata.[2–4] Finalistic movements (e.g., elaborated movements clearly resembling an identifiable

Supplemental data at Neurology.org/nn

daytime activity such as manipulation of objects) were not registered in our patient's video-PSG, although they were clearly present by clinical history.

This disorder provides an intriguing link between autoimmunity and neurodegeneration. Previously reported patients had IgG4 antibodies against IgLON5, and, as in our case, all patients that were HLA genotyped had the same alleles: HLA-DQB1*0501 and HLA-DRB*1001. An unexpected finding in the autopsy of 2 patients was the detection of neuronal-specific tau deposits in the hypothalamus and tegmentum of the brainstem in a distribution different from known tauopathies[5,6] and absent signs of inflammation.[2] Our patient is the first with abnormal CSF findings, although the pleocytosis was mild.

In IgLON5 encephalopathy, the most prominent and usually the first manifestation is the sleep dysfunction, so all medical specialties involved with sleep medicine should be aware of this entity. In addition, chronic progression of symptoms such as chorea, dementia, dysarthria, dysphagia, ataxia, dysautonomia, and vertical gaze paresis, which variably associate with IgLON5 encephalopathy, also occur in neurodegenerative diseases (e.g., multiple system atrophy, progressive supranuclear palsy).[7] In our experience, if sleep symptoms are overlooked, this disease is usually misdiagnosed.

From the Neurology Division (M.M.S., T.A., R.G.C., M.S.H., C.H.M., L.O., M.B., R.C.A., L.A.S., R.N.), Hospital das Clínicas, São Paulo University (HC/FMUSP), Brazil; August Pi I Sunyer Biomedical Research Institute (IDIBAPS) (L.S., J.D., F.G.), Barcelona, Spain; Hospital Clínic (C.G., J.S., F.G.), University of Barcelona, Spain; Department of Neurology (J.D.), University of Pennsylvania, Philadelphia; and Catalan Institution for Research and Advanced Studies (ICREA) (J.D.), Barcelona, Spain.

Author contributions: Dr. Simabukuro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Simabukuro, Dalmau, Graus. Acquisition of data: Simabukuro, Azevedo Soster, Alves, Haddad, Cury, Oliveira, Adoni, Boaventura, Moreira. Analysis and interpretation of data: Dalmau, Graus, Gaig, Santamaría, Simabukuro, Azevedo Soster, Alves, Sabater. Drafting of the manuscript: Simabukuro, Dalmau, Graus. Critical revision of the manuscript for important intellectual content: Simabukuro, Nitrini, Graus, Gaig, Santamaría, Dalmau. Administrative, technical, or material support: Dalmau, Graus, Gaig, Santamaría, Haddad, Cury, Simabukuro, Azevedo Soster, Alves, Sabater. Study supervision: Simabukuro, Nitrini, Dalmau, Graus.

Acknowledgment: The authors thank Dr. Leandro Tavares Lucato (Radiology Institute, Hospital das Clínicas, São Paulo University) for reviewing neuroradiologic images and Dr. Maira Okada de Oliveira (Behavioral and Cognitive Neurology Unit, Hospital das Clínicas, São Paulo University) for the neuropsychological testing data.

Study funding: This work was supported in part by NIH grant RO1NS077851, and Fondo de Investigaciones Sanitarias, Instituto Carlos III PI11/01780 (Dr. Dalmau). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosures: M. Simabukuro received travel funding from Centro de Estudos de Neurologia Prof. Dr. Antonio Branco Lefèvre and World Congress of Brain, Behavior and Emotion. L. Sabater reports no disclosures. T. Adoni received speaker honoraria from Teva and Biogen Idec and is an associate editor for Arquivos de Neuro-Psiquiatria. R.G. Cury, M.S. Haddad, C.H. Moreira, L. Oliveira, M. Boaventura, R.C. Alves, and L. Azevedo Soster report no disclosures. R. Nitrini is on the advisory board for Janssen-Cilag and Brazilian Nutricia; received travel funding from Novartis; is an editor for Dementia & Neuropsychologia; is on editorial board for Alzheimer's Disease and Associated Disorders and International Journal of Alzheimer's Disease; has spoken for Novartis and Danone (Nutricia); and has received research support from FAPESP. C. Gaig and J. Santamaría report no disclosures. J. Dalmau is the editor of Neurology: Neuroimmunology & Neuroinflammation; is on the editorial board for Neurology UpToDate; holds patents for and receives royalties from autoantibody test, NMDA receptor autoantibody test; has patents pending for GABA(B) receptor autoantibody test, GABA(A) receptor autoantibody test, DPPX autoantibody test, IgLON5 autoantibody test; has consulted for Advance Medical; and received research support from Euroimmun, NIH, NIMH, and Instituto Carlos III, AGUR. F. Graus is on the editorial board for Lancet Neurology and received research support from Fondo Investigaciones Santitarias. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was paid by the authors.

Received February 23, 2015. Accepted in final form May 20, 2015.

Correspondence to Dr. Simabukuro: mateus.simabukuro@hc.fm.usp.br

1. Högl B, Heidbreder A, Santamaria J, Graus F, Poewe W. IgLON5 autoimmunity and abnormal behaviours during sleep. Lancet 2015;385:1590.
2. Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol 2014;13:575–586.
3. Lugaresi E, Provini F. Agrypnia excitata: clinical features and pathophysiological implications. Sleep Med Rev 2001;5:313–332.
4. Gaig C, Iranzo A, Santamarí J, Dalmau J, Graus F. Sleep disorder associated with antibodies to IgLON5: parasomnia or agrypnia?—Authors' reply. Lancet Neurol 2014;13: 864–865.
5. Spillantini MG, Goedert M. Tau pathology and neurodegeneration. Lancet Neurol 2013;12:609–622.
6. Ludolph AC, Kassubek J, Landwehrmeyer BG, et al; Reisensburg Working Group for Tauopathies with Parkinsonism. Tauopathies with parkinsonism: clinical spectrum, neuropathologic basis, biological markers, and treatment options. Eur J Neurol 2009;16:297–309.
7. Fahn S, Jankovic J, Hallett M. Principles and Practice of Movement Disorders: Expert Consult, 2nd ed. Edinburgh, New York: Saunders; 2011.