IgLON5-mediated neurodegeneration is a differential diagnosis of CNS Whipple disease

A 49-year-old man developed cold intolerance as an isolated symptom 2 years prior to presentation. At age 48, he developed jerks in the trunk and lower limbs during the day and tapping movements in the arms during sleep. After 6 months, sleep disturbance worsened with talking and gesticulations, culminating in sleeping 1–3 hours per night with associated daytime somnolence. He developed mild slurred speech, hypersalivation, and dysphagia. He reported poor memory but was able to continue driving and working. He had been diagnosed with obstructive sleep apnea 4 years prior.

On examination, the patient was alert with mildly impaired cognition (Addenbrooke Cognitive Examination–III 87/100). Vertical and horizontal saccades were hypometric but of normal velocity. At rest, he had subtle, continuous, low-amplitude regular contractions of the mentalis, tongue, and frontalis. Rhythmic palatal movements at a frequency of ~1 Hz were also present (video). Intermittent, isolated, truncal flexion movements at the hip occurring every 2–4 seconds were observed with the patient lying, sitting, or standing.

Brain MRI was normal. 18-FDG PET scan showed striatal and brainstem hypermetabolism (figure). CSF and serum antineuronal antibodies (anti-GAD, Ma1/Ma2, CRMP-5, amphiphysin, Yo, PCA2, Hu, Ri) and surface neuronal antibodies (NMDA, CASPR2, LGI-1, GABA-B, AMPA1, AMPA2) were negative. IgLON5 antibodies were positive with titers 1:3,200 in serum and 1:100 in CSF. CSF oligoclonal bands and 14-3-3 protein and PCR for Tropheryma whippelii and syphilis were negative. Familial fatal insomnia and Huntington disease were ruled out by genetic analysis. HLA-DRB1*10:01 and HLA-DQB1*05:01 were positive. A polysomnographic study revealed an apnea/hypopnea index of 2.8, 33% sleep efficiency, and a total of 30 minutes REM sleep.

Stereotactic brain biopsy was arranged because of the initial suspicion of CNS Whipple disease, before the IgLON5 Ab result was available. The frontal cortex showed mild thickening of the meninges with scattered histiocytes, CD3+ T lymphocytes around blood vessels, increased CD68+ and CD163+ microglia in cortical layer 1, and mild gliosis and focal edema in layer 1, which was more marked in deeper layers (figure). The cerebellar biopsy also showed patchy edema and gliosis as well as patchy loss of Purkinje cells. Immunostaining for tau, a-synuclein, β-amyloid, phosphorylated-TDP43, and P62 were all negative. There were no microorganisms seen and PCR for T whippelii was negative. Treatment was initiated with plasma exchange, IV immunoglobulin, and rituximab.

Discussion

Cold intolerance, myorhythmia, and myoclonus as early features of IgLON5-mediated neurodegeneration are novel findings. Cold intolerance is a novel symptom, and may be related to hypothalamic pathology. In anti-IgLON5 disease, the most common initial
symptoms include disturbances of sleep, gait, and bulbar function. Parkinsonism, chorea, myoclonus, and focal dystonia have been observed in nearly two-thirds of patients.\textsuperscript{1–3} A progressive supranuclear palsy–like case with orolingual myorhythmia but without sleep disturbance has been reported.\textsuperscript{2} The combination of myorhythmia, sleep disorder, and hypothalamic dysfunction has a narrow differential diagnosis, in particular CNS Whipple disease and familial fatal insomnia. IgLON5 should be included in the differential diagnosis of this rare syndrome because of its potential therapeutic implications. The 18-FDG-PET findings of increased striatal and brainstem metabolism are novel and unusual for a neurodegenerative disorder. Interestingly, striatal without brainstem hypermetabolism has been reported in another patient with IgLON5.\textsuperscript{4}

The neuropathology of IgLON5 disease has been reported in 7 patients postmortem with the universal presence of hyperphosphorylated tau in subcortical structures including the hypothalamus and brainstem, but notably absent or minimal in cerebral or cerebellar cortex.\textsuperscript{5} A pattern of tau deposition in the temporal cortex, hypothalamus, and locus ceruleus but without involvement of other brainstem nuclei has been reported.\textsuperscript{5} Microglial TDP-43 pathology and perivascular CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells and CD20\textsuperscript{+} B cells have been reported in only a single postmortem case.\textsuperscript{6}

Figure Neuroimaging, pathologic, and tremor analysis findings in IgLON5-mediated disease

18-FDG-PET shows symmetric hypermetabolism in the tegmentum between the pons and medulla oblongata (A) and bilateral striatal hypermetabolism (B). Pathology of frontal cortex of the patient stained with hematoxylin & eosin shows gliosis in the gray and white matter interface (C), CD163\textsuperscript{+} cells demonstrating microglial activation and increased numbers of microglia around blood vessels (D), and CD3\textsuperscript{+} T cells in perivascular location (E) (magnification ×100 for all). Tremor analysis and surface EMG recordings of the face and right upper limb muscles over 16 seconds demonstrate a 0.5–1 Hz tremor in left zygomaticus, genioglossus, and right mentalis consistent with cranial myorhythmia (F).
A current debate is whether IgLON5 disease is primarily a neurodegenerative process mediated by tau deposition with a secondary autoimmune response, or alternatively a primary autoimmune process leading to secondary tau deposition.7 Our patient is the first to demonstrate in vivo evidence of an inflammatory infiltrate in the absence of tau staining in the biopsied regions. While we cannot exclude tau pathology in nonbiopsied, deep structures, our findings support that inflammation can be seen in IgLON5. One possible explanation for our novel pathologic findings is that our patient is only ∼4 years into his illness with a relatively early or mild phenotype, as opposed to the mean of 9 years post disease onset described in the autopsy cases reported so far.5 There is emerging evidence of some patients with IgLON5 disease responding to immunotherapy.2 The biopsy findings in our patient provide evidence that neuroinflammation can occur in IgLON5-associated disease.

**Author contributions**
Hugo Morales: study concept and design, acquisition and interpretation of data; writing first draft and final version of the manuscript. Belinda Cruse: study concept and design, acquisition and interpretation of data; writing first draft, critical revision of final manuscript for intellectual content. Alessandro Fois: study concept and design, acquisition and interpretation of data; writing first draft, critical revision of final manuscript for intellectual content. Ming-Wei: study concept and design, acquisition and interpretation of data; study supervision, critical revision of final manuscript for intellectual content. Jocelyn Jiang: study concept and design, acquisition and interpretation of data; study supervision, critical revision of final manuscript for intellectual content. Dev Banerjee: acquisition of data, interpretation of data, critical revision of final manuscript for intellectual content. Ron Grunstein: acquisition of data, interpretation of data, critical revision of final manuscript for intellectual content. Winny Varikatt: acquisition of data, interpretation of data, critical revision of final manuscript for intellectual content. Michael Rodriguez: acquisition of data, interpretation of data, critical revision of final manuscript for intellectual content. Claire Shepherd: acquisition of data, interpretation of data, study supervision, critical revision of final manuscript for intellectual content. Victor Fung: study concept and design, interpretation of data, study supervision, critical revision of final manuscript for intellectual content.

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**References**
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