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IGLON5 Frequency in Idiopathic REM Sleep Behavior Disorder

A Multicenter Study

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Abstract

Background and Objectives

Idiopathic/isolated REM sleep behavior disorder (iRBD) has been strongly linked to neurodegenerative synucleinopathies such as Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. However, there have been increasing reports of RBD as a presenting feature of serious and treatable autoimmune syndromes, particularly IGLON5. This study's objective was to investigate the frequency of autoantibodies in a large cohort of participants with iRBD.

Methods

Participants were enrolled in the North American Prodromal Synucleinopathy cohort with polysomnography-confirmed iRBD, free of parkinsonism and dementia. Plasma samples were systematically screened for the autoantibodies IGLON5, DPPX, LGI1, and CASPR2 using plasma IgG cell-based assay. Positive or equivocal results were confirmed by repeat testing, plus tissue-based indirect immunofluorescence assay for IGLON5.

Results

Of 339 samples analyzed, 3 participants (0.9%) had confirmed positive IGLON5 autoantibodies in the cell-based assay, which were confirmed by the tissue-based assay. An additional participant was positive for CASPR2 with low titer by cell-based assay only (of lower clinical certainty). These cases exhibited a variety of symptoms including dream enactment, cognitive decline, autonomic dysfunction, and motor symptoms. In 1 IGLON5 case and the CASPR2 case, evolution was suggestive of typical synucleinopathy, suggesting the possibility that findings were incidental. However, 2 participants with IGLON5 died before diagnosis was clinically suspected, with a final clinical picture highly suggestive of autoimmune disease.

Discussion

Our finding that nearly 1% of a large iRBD cohort may have a serious but potentially treatable autoantibody syndrome has important clinical implications. In particular, it raises the question

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Glossary

CBA = cell-based assay; **FITC** = fluorescein isothiocyanate–conjugated; **IFA** = immunofluorescence assay; **iRBD** = idiopathic/isolated REM sleep behavior disorder; **MoCA** = Montreal Cognitive Assessment; **MSA** = multiple system atrophy; **NAPS** = North American Prodromal Synucleinopathy; **PD** = Parkinson disease; **RBD** = REM sleep behavior disorder.

of whether autoantibody testing for IGLON-5-IgG should be widely implemented for participants with iRBD, considering the difficulty in diagnosis of autoimmune diseases, their response to treatment, and the potential for rapid disease progression. However, any routine testing protocol will also have to consider costs and potential adverse effects of false-positive findings.

Trial Registration Information

NCT03623672

Introduction

REM sleep behavior disorder (RBD) is a parasomnia characterized by loss of the normal paralysis that accompanies REM sleep, such that patients 'act out' their dreams.[1] RBD is generally considered to be a strong marker of neurodegenerative synucleinopathy; most of the patients with idiopathic/isolated RBD eventually develop either Parkinson disease (PD), dementia with Lewy bodies, or multiple system atrophy (MSA).[2] The association with neurodegenerative synucleinopathy is highly specific; an autopsy study found that 98% of cases of polysomnography-confirmed RBD had pathologic synuclein deposition.[3]

Recently, there have been an increasing number of reports linking RBD with antibody-mediated syndromes, most notably those associated with IGLON5 and voltage-gated potassium channels (CASPR2, LGI1, and DPPX).[4-8] In these cases, RBD symptoms often occur as part of a generalized sleep-wake disturbance, sometimes presenting subacutely in association with prominent sleep apnea and non-REM parasomnia. Polysomnograms generally detect severe disruption of sleep stages (termed variably as undifferentiated REM sleep, agrypnia excitata, etc). Response to treatment varies, but some show substantial improvement on immunosuppressive therapy.[9]

Given that these conditions may constitute a significant and potentially reversible cause of neurodegeneration, it is vital to assess how commonly they might occur in RBD, especially among those who are not identified as having a classic antibody-mediated syndrome. To this end, we undertook a systematic screening for autoantibodies in a large cohort of participants with iRBD enrolled in the North American Prodromal Synucleinopathy (NAPS) study.

Methods

All participants were enrolled in the NAPS cohort.[10] This cohort follows participants with polysomnography-confirmed iRBD. All participants are free of parkinsonism and dementia and have no known alternate explanation for their RBD (i.e., any participant with a known antibody-mediated RBD would be excluded). Baseline characteristics of the cohort and details of clinical assessment procedures have been described in detail elsewhere.[10] All participants provided informed consent to participate in the study, which received approval from the respective institutional research ethics boards.

Antibody Testing

Sampling was performed on 500-uL aliquots of plasma that had been collected between 2018 and 2022 and stored at −80°C. Plasma IgG testing was undertaken by the cell-based assay (CBA) that used slides consisting of a mosaic of biochips, each chip consisting of human embryonic kidney 293 cells transfected with complementary DNA for IGLON5, DPPX, LGI1, or CASPR2. The slides were fixed with 1% formalin and stored at 4°C (Euroimmun AG, Lubeck, Germany). CBA was performed using participant plasma (1:10 dilution), incubated with the transfected cells. The cells were then washed and exposed to fluorescein isothiocyanate–conjugated (FITC) goat anti-human IgG (Southern Biotech, Birmingham, AL). Samples positive or equivocal by CBA underwent repeat CBA testing to clarify results. Samples yielding a positive result for IGLON5-IgG by CBA were then tested by the murine tissue-based indirect immunofluorescence assay (IFA), which used a composite substrate of mouse hippocampus, cerebral cortex, cerebellum, basal ganglia, thalamus, kidney, and stomach. 4-micrometer frozen cryosections were fixed, blocked, and incubated with participant plasma for 40 minutes and then with FITC secondary antibody. Titrations to the end point by doubling dilutions were undertaken (normal, ≤1:240).

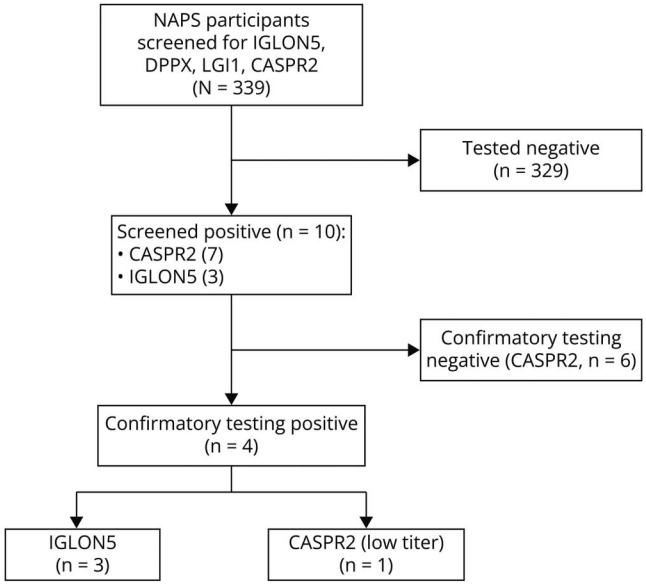
Data Availability

The principal author (RP) has full access to the data used in the analyses in the study. The full deidentified data set will be made accessible after standard written request according to NAPS guidelines.

Results

A total of 339 samples were analyzed, of which 329 were negative in all assays (Figure for flow diagram). 7 tested equivocally

Figure Participant Flow and Testing Results



positive on preliminary assay for CASPR2; in 6 cases, these results were not confirmed on cell-based assay repeat testing, and 1 case was positive on low titer by cell-based assay. A total of 3 participants (0.9%) were positive for IGLON5. Details of these cases, as well as the low-titer CASPR2 case, are given further.

Case 1—IGLON5

Patient 1 was a 70-year-old man who reported a 3-year history of dream enactment behavior. He was known to have obstructive sleep apnea treated with CPAP. The diagnosis of obstructive sleep apnea was made by an outside sleep laboratory 3 years earlier (details of this trace are unavailable). CPAP had been provided with good compliance. Our baseline polysomnogram (performed on CPAP) showed overall good control of obstructive sleep apnea, with AHI of 5.9, and a total of 4 minutes with oxygen saturation less than 90%. Sleep efficiency was poor (47%), and he took 2 hours to fall asleep. No stridor was either reported on history or observed on our PSG. No elements of NREM parasomnia were evident at time of initial clinical visit, PSG, or baseline research visit. On video PSG, there were no pseudo-purposeful movements during NREM sleep, but during REM sleep, numerous twitches of hands and fingers and face were observed (there were no aggressive dream enactment behaviors observed). At baseline research visit, there was mild insomnia without somnolence (this reflected an improvement over the past 3 years, during which he had been troubled by severe sleep-onset insomnia). He had been previously prescribed venlafaxine, without clear changes in dream enactment when medications were stopped or started. Medical history was significant for type 2 diabetes. His father had dementia, although the specific diagnosis and clinical features were unknown.

At the baseline visit, he reported numerous autonomic symptoms, including orthostatic intolerance (without objective blood pressure drop on examination), urinary frequency, severe erectile dysfunction, and constipation. He had longstanding symptoms of depression and anxiety. Motor symptoms included difficulty with swallowing, drooling, and speech/articulation, with subjective gait slowing and imbalance. Baseline motor examination revealed only subtle hypomimia with a quiet voice, equivocal slowing of leg movements, and subtle gait slowing (total MDS-UPDRS Part III score = 5). There was no rigidity, bradykinesia, or cerebellar dysfunction. Quantitative motor testing revealed slowed alternate tap test and reduced Purdue PegBoard performance. Olfactory testing was normal. Color vision was normal (Farnsworth-Munsell 100 = 56). Although his Montreal Cognitive Assessment (MoCA) score was low at 20, this was confounded by education and language barrier; cognition according to both the participant and his family was unchanged from his usual state.

One year later, sleep symptoms remained largely unchanged, with some improvement in depression, anxiety, and autonomic symptoms. His bed partner noted rare episodes of sleepwalking over the past year, suggesting possible NREM parasomnia. Motor examination was improved, with the MDS-UPDRS Part III score now only 1. Quantitative testing was also improved to within the low-normal range, and olfaction remained normal.

However, on the third visit (in 2020), symptoms had worsened. The frequency of dream enactment had increased to almost nightly, without change in the character of dream enactment. There was no worsening of insomnia or somnolence. All autonomic symptoms had recurred, and he now had a postural systolic blood pressure drop of 26 mm Hg (supine to standing at 3 minutes) with symptoms of urinary retention. He noted worsening of bulbar and gait symptoms. Examination revealed nonspecific generalized slowing/clumsiness, without decrementing bradykinesia or clear cerebellar signs. There was no rigidity or tremor. He had reduced postural stability. We observed no extraocular movement abnormalities. The MDS-UPDRS Part II score was 12. We raised concerns about possible early evolution to multiple system atrophy—cerebellar type—although he did not meet criteria for MSA at that time. Although we proposed closer research-based follow-up, he elected to return to his clinical neurologist and declined further research follow-up (he provided permission to contact him by telephone if needed).

IGLON5-IgG was positive by cell-based assay, and the distinctive staining pattern was also detected by tissue IFA (end-point dilution was 1:1920). On receipt of testing results, the participant and his treating team were promptly contacted. Unfortunately, since the last visit, he had continued to decline neurologically. His clinical neurology team gave a working diagnosis of MSA-C, based mainly on symptoms of orthostatic hypotension, bulbar symptoms, and gait instability. However, they noted numerous atypical features, most prominently atypical and nonlocalizable horizontal gaze abnormalities, very severe bulbar symptoms disproportionate to the remainder of the examination, and the

later development of choreiform movements in the lower limbs. He developed aspiration pneumonia and was admitted twice to hospital. With the second admission, he contracted comorbid COVID-19 and died soon afterward, 6 months before antibody test results became available. No autopsy was performed.

Case 2—IGLON5

Patient 2 was a 75-year-old man who presented with a 15-year history of dream enactment behavior, along with occasional sleepwalking. A PSG in 2006 performed in an outside center had noted abnormal movements during REM sleep, but no diagnosis of RBD was made at that time. At the baseline visit in our center, he reported slight insomnia and slight daytime somnolence (although the Epworth Sleepiness Scale score was only 4). PSG in our center noted mild obstructive sleep apnea with AHI of 9 and a minimum oxygen saturation of 91%. CPAP was provided at this time, and the participant remained compliant on this. Medical history was otherwise significant for type 2 diabetes. There was no family history of RBD, dementia, or parkinsonism.

At baseline, he reported mild cognitive symptoms, particularly with memory and executive function. Autonomic symptoms included slight urinary frequency and occasional constipation without symptoms of orthostatic intolerance. There were no motor symptoms except for slight swallowing difficulty. He had a systolic blood pressure drop of 21 mm Hg from supine to standing at 3 minutes. The MoCA score was 25/30. Neurologic examination was normal. Motor examination was entirely normal with the MDS-UPDRS Part III score of 0. Quantitative motor testing revealed normal alternate tap test and equivocally reduced Purdue Pegboard performance. Olfaction was reduced, with a Brief Smell Identification Test score of 5/12. Color vision testing was abnormal (FM-100 = 284).

IGLON5-IgG was positive by cell-based assay, and the distinctive staining pattern was also detected by tissue IFA (end-point dilution was 1:960). However, 4 months after baseline visit, he was diagnosed with esophageal cancer, and he underwent an esophagectomy. This was conducted successfully, with no noted intraoperative complications. However, postoperative course was complicated by severe delirium. After discharge home, there was significant deterioration in cognitive abilities. He developed severe circadian disruption. Frequency of RBD episodes increased. As the neurologic disorder progressed, he required intubation, subsequently became comatose, and eventually died. No autopsy was performed.

Case 3—IGLON5 Seropositivity With Alpha-Synucleinopathy

Clinical details of Case 3 have been withheld from publication at participant request. IGLON5-IgG was positive by cell-based assay, and the distinctive staining pattern was also detected by tissue IFA (end-point dilution was 1:4,800). This participant had numerous clinical and radiologic markers of synucleinopathy, including a positive synuclein seeding assay, and had no improvement with immunotherapy against IGLON5.

Other Antibody Findings

Results of DPPX and LGI-1 were negative in all cases. 1 case demonstrated equivocal CASPR2 seropositivity, with a result profile that suggested a possible incidental/false-positive finding. This participant had developed classic tremor-dominant parkinsonism responsive to levodopa with olfactory loss. Antibody testing performed on baseline samples (collected 3 years before PD diagnosis) found positivity of low-titer CASPR2 (1:10, considered nonspecific for neurologic autoimmunity) and low-titer anti-GAD65 (0.08) positivity. Of note, over the previous year, he had underwent an extensive systemic workup for a general medical condition, which involved repeated CT scans of the chest, abdomen, and pelvis. None showed evidence for malignancy (a previous colonoscopy was also negative). The possibility of offering immunotherapy was discussed, but the participant declined. As of the last visit, cognitive, motor, autonomic, and sleep/RBD symptoms had remained stable.

Discussion

The central finding of this study was that just under 1% of a large research cohort of people with idiopathic RBD may have had an underlying serious, potentially treatable IGLON5 autoimmunity syndrome. Two participants died before IGLON5 antibody positivity was known, without the diagnosis being previously suspected clinically.

These results raise an important question: should patients with iRBD undergo routine testing for autoantibodies, or would a more selective approach suffice? Regarding a selective approach, delving deeper into the clinical histories, there may have been some diagnostic clues, albeit with uncertain predictive value. For instance, 3 of 4 participants were diagnosed with obstructive sleep apnea, which is highly prevalent in these autoimmune syndromes (none had central apnea). However, 55% of the remaining NAPS cohort also had a sleep apnea diagnosis.[10] Two cases had some NREM parasomnia features, which are classically seen in IGLON5-associated disease. However, 11% of the same cohort has reported sleepwalking or other NREM features alongside their RBD. Absence of hyposmia might have been a very useful clue because hyposmia is a strong marker of Lewy body disease; however, only case 1 had normal olfaction. While both fatal cases experienced a period of rapid decline, this was not apparent on initial visits because case 1 exhibited spontaneous improvement between baseline and 1 year and case 2's decline occurred after surgery for cancer, confounding the interpretation. In summary, both cases 1 and 2 had several atypical features at some point in their illness, which were arguably of high enough specificity to argue that a selective approach to testing could be warranted.

The second option would be to routinely test all patients, although this raises important concerns about cost, a low pretest probability (i.e., 0.9% positivity rate in our study), and potential harm related to incidental or false-positive findings.

In particular, one of the IGLON5 cases and the single positive CASPR2 case have followed a clinical trajectory more akin to what is typically seen in synucleinopathy, including an evolution to classic PD in one. This may suggest that these positive antibody tests were only incidental findings.

Regarding treatment decisions in the case of a positive test, detecting IGLON5-IgG by both cell-based and tissue-based assays provides a high level of confidence in the serologic diagnosis, even in the absence of CSF antibody testing.[9] IGLON5 autoimmunity seems to occur in the borderlands of neurodegeneration and autoimmunity. Pathologic studies have revealed 3R/4R tauopathy, which could support a primary degenerative etiology.[11] However, systemic screens of patients with clinical 4R tauopathy have not found positive tests, and functional effects of IGLON5-IgGs in neuronal cell cultures and responses to immunotherapy in some patients are consistent with a primary autoimmune etiology.[12,13] This might suggest that IGLON-5 results are relatively unlikely to be incidental and so warranted consideration of a trial of treatment in that case. By contrast, the CASPR2 antibody was of very low titer and is, therefore, unlikely to be of clinical significance, given evolution to classic PD with levodopa responsivity and absence of other syndromic autoimmune features; CASPR2 antibody positivity at 1:10 titer may have lower predictive value for an autoimmune diagnosis than titers of 1:100.

In conclusion, we have found potentially treatable positive IGLON5 syndromes in 1% of patients with iRBD in whom the diagnosis was not clinically suspected. These findings raise considerations of implementing screening protocols for patients with iRBD, particularly those who do not present with features indicative of underlying synucleinopathies.

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Appendix *(continued)*

Name	Location	Contribution
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