Title

Predicting alpha-synuclein pathology by REM sleep behavior disorder diagnosis

Authors

Shprecher, David R
Adler, Charles H
Zhang, Nan
et al.

Publication Date

2018-10-01

DOI

10.1016/j.parkreldis.2018.05.020

Peer reviewed

HHS Public Access

Author manuscript

Parkinsonism Relat Disord. Author manuscript; available in PMC 2021 February 01.

Published in final edited form as:

Parkinsonism Relat Disord. 2018 October ; 55: 92–96. doi:10.1016/j.parkreldis.2018.05.020.

Predicting alpha-synuclein pathology by REM sleep behavior disorder diagnosis

David R. Shprecher, DO MSci[1], **Charles H. Adler, MD PhD**[2], **Nan Zhang, MS**[3], **Joseph G Hentz, MS**[3], **Geidy E. Serrano, PhD**[4], **Brittany N. Dugger, PhD**[5], **Holly A. Shill, MD**[6], **Rodolfo Savica, MD PhD**[7], **John N. Caviness, MD**[2], **Marwan N. Sabbagh, MD**[6], **Christine M. Belden, PsyD**[1], **Erika Driver-Dunckley, MD**[2], **Shyamal H. Mehta, MD PhD**[2], **Lucia I. Sue, BS**[4], **Kathryn J. Davis, BA**[4], **Edward Zamrini, MD**[1], **Thomas G. Beach, MD, PhD**[4]

[1]Cleo Roberts Center, Banner Sun Health Research Institute, Sun City, AZ, United States

[2]Department of Neurology, Mayo Clinic College of Medicine, Scottsdale, AZ, United States

[3]Department of Biostatistics, Mayo Clinic College of Medicine, Scottsdale, AZ, United States

[4]Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, AZ, United States

[5]University of California Davis College of Medicine, Davis, CA, United States

[6]Barrow Neurological Institute, Phoenix, AZ, United States; University of Arizona College of Medicine-Phoenix

[7]Department of Neurology, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN, United States

Abstract

Inability to accurately diagnose Lewy type alpha- synucleinopathy (LTS) pre-mortem has been a major obstacle to clinical care and research. Probable REM sleep behavior disorder (PRBD) diagnosed with support of instruments such as the Mayo Sleep Questionnaire (MSQ) may provide

Corresponding Author: David Shprecher, DO Msci, Banner Sun Health Research Institute, 10515 W Santa Fe Dr, Sun City, AZ 85351, Tel 623-832-6530/Fax 623-832-6504/ david.shprecher@bannerhealth.com.

Author Roles:
DRS: 1A, 1B, 2A, 3A
CHA: 1B, 1C, 2A, 2C, 3B
NZ: 1B, 2A, 2B, 3B
JGH: 1B, 2A, 2B, 3B
GS: 1B, 1C, 3B
BD: 1C, 3B
HS: 1C, 3B
RS: 3B
JC: 1C, 3B
MS: 1C, 3B
CB: 1C, 3B
ED-D: 1C, 3B
SHM: 1C, 3B
LS: 1C
EZ: 1C
TGB: 1A, 1B, 1C, 2A, 2C, 3B
1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

a cost effective means of predicting LTS. Since 2007, 602 subjects in the Arizona Study of Aging and Neurodegenerative Disorders had clinician assessment for PRBD (298 with, 304 without support of the MSQ), completed cognitive and movement examinations, and had neuropathological assessment. Mean age at death was 84.8 years. Histological evidence of LTS was found in 80/101(79.2%) cases with PRBD and 198/501 (39.5%) without PRBD ($p < 0.001$). Overall sensitivity for predicting LTS by PRBD diagnosis was 28.8%, specificity 93.5%, positive predictive value (PPV) 79.2%, negative predictive value (NPV) 60.5%. Diagnosis of PRBD was less frequently present in subjects without LTS [4/105 (3.8%) of healthy controls, 42/255 (16.5%) AD, 2/33 (6.1%) progressive supranuclear palsy (PSP) without LTS] than in subjects with LTS [11/46 (23.9%) DLB, 58/104 (55.8%) PD, and 4/16 (25.0%) PSP with LTS.] PRBD was not present in any of 46 subjects with incidental Lewy body disease (ILBD). MSQ-supported diagnosis of PRBD appears useful for predicting LTS in manifest neurodegenerative disease, but not necessarily ILBD. Additional prospective autopsy research, including well-characterized polysomnogram-confirmed RBD subjects, is needed to elucidate the earliest tissue abnormalities in the “idiopathic” (premotor/pre-dementia) stage of RBD.

Keywords

Parkinson disease; Parkinson disease dementia; Dementia with Lewy bodies; REM sleep behavior disorder

Introduction

Neurodegenerative disease clinical care and research have been hindered by the lack of any test that can accurately diagnose underlying conditions during an individual’s lifetime (pre-mortem). Although amyloid PET scans are available (and tau ligands are in development), an *in-vivo* test to identify alpha-synuclein pathology remains elusive. Idiopathic REM sleep behavior disorder (iRBD), a condition characterized by violent dream enactment behavior and loss of REM atonia, has emerged as a strong known predictor of a final clinicopathological diagnosis of a Lewy type alpha-synucleinopathy (LTS): either Parkinson disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), or pure autonomic failure [1–5]. A definite diagnosis of iRBD requires a polysomnogram (PSG) to confirm loss of REM atonia, and the absence of alternative explanations for apparent dream enactment should be established [6], but these measures are costly and time consuming. Furthermore, PSG may not be sufficient to confirm definite RBD diagnosis if the report does not document dream enactment plus REM without atonia. Clinicians may therefore rely on probable RBD (PRBD) diagnosis by history to support neurodegenerative disease diagnosis. This approach may be justified by findings of an autopsy study on 172 neurodegenerative disease subjects, where 98% of those with PSG confirmed definite RBD, and 94% of those with probable RBD by history, had autopsy-proven LTS [1]. In the study, clinician diagnosis was supported by use of a validated screening instrument. Among these, the Mayo Sleep Questionnaire (MSQ) is a 16-item scale that screens for sleep disorders by asking if a behavior has been observed at least 3 times in the past [7]. It has been copyrighted by Mayo Foundation, with permission granted free of charge to download for patient care and non-commercial research from http://www.mayoclinic.org/documents/msq-copyrightfinal-pdf/

doc-20079462. The core question about dream enactment has shown, in a healthcare provider population, 100% sensitivity and 95% specificity to determine the presence of PSG-confirmed RBD, when completed with input from an informant [7,8]. In contrast, sensitivity and specificity were 98% and 74% when an informant was not required. Use of an informant may therefore be expected to improve utility of the MSQ in predicting final clinicopathological diagnosis.

We aimed to determine the sensitivity, specificity and predictive values of MSQ-supported clinician diagnosis of PRBD in predicting the histological presence of LTS in a broader, less-selected, volunteer elderly population. Furthermore, we investigated whether use of an informant in completion of the MSQ improved sensitivity and specificity of clinician diagnosis of PRBD in predicting LTS [9].

Materials and Methods

Subjects

All human subjects research was completed under Western Institutional Review Board approval and after written informed consent/assent of subjects and their legally authorized representatives. Since 2007, 602 subjects in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) had completed standardized movement and cognitive examinations, including a clinician assessment for presence or absence of PRBD, and had come to autopsy. Of these, 298 had at least one completed MSQ available to support the PRBD assessment (235 with participation of a caregiver or bed partner informant.) Methods have been previously described [10]. A final clinical movement and cognitive diagnosis for all subjects (including presence or absence of PRBD) was assigned by consensus conference at the time of death by review of all clinical data, including AZSAND standardized clinical assessments, private medical records and informant completed MSQs. Following autopsy and neuropathological examination, a final clinicopathological diagnosis was assigned to each case according to consensus criteria [11,12] based upon all clinical and neuropathological data. The topographical distribution of LTS was classified using the Unified Staging System for Lewy Body Disorders (USSLB) [13]. Those with LTS not meeting criteria for PD, DLB, AD or incidental Lewy body disease (ILBD) (for example, vascular dementia with LTS) were labeled LTS NOS. The majority of MSQs were completed at the time of the clinical examinations. Twenty-five cases had an informant MSQ completed by telephone post-mortem. Of the 298 subjects with MSQ responses, 184 completed more than one MSQ over time. Of these, 39 subjects had a final answer to the question “have you ever seen the patient appear to ‘act out his/her dreams’ while sleeping? (Punched or flailed arms in the air, shouted or screamed)” that differed from the original response (17 where ‘no’ became ‘yes’, and 22 where ‘yes’ became ‘no’.) For the purposes of this study, a subject was considered to have PRBD based on clinician review of all clinical data- including final responses on the MSQ to the question, “Have you ever seen the patient appear to ‘act out his/her dreams’ while sleeping? (Punched or flailed arms in the air, shouted or screamed).”[8]

Statistical analysis

The demographics and final clinicopathological diagnosis of cases with and without clinician diagnosed PRBD were compared using two sample t-tests, Wilcoxon rank sum test, Chi-square test or Fisher's exact test when applicable. The population was divided into 3 groups: those without MSQ, those with MSQ (but no informant), and those with informant-supported MSQ. Sensitivity, specificity, positive predictive value and negative predictive value of final clinical diagnosis of PRBD for predicting LTS in each group were calculated separately and compared across the three groups using a Chi-square test.

Results

Of the 602 subjects with a clinical assessment for PRBD available, 45.2% were female, and mean age at death was 84.8 (SD 7.9). Most cases had mixed pathology, with the most common clinicopathological diagnoses (regardless of PRBD status) being AD in 255 (42.4%), 104 PD (17.3%), and 46 DLB (7.6%), while 105 (17.4%) were normal on their final cognitive and movement assessment. Where overlapping diagnoses were present (i.e., PD/AD, DLB/AD), these are reported by separate categories below (categories are not mutually exclusive). Comparing cases with and without PRBD, mean age at death was 80.7 (7.6) vs 85.6 (7.7) ($p<0.0001$), and sex distribution was 23.8% vs 49.5% female ($p=<0.0001$), respectively. Excluding healthy controls and ILBD subjects, mean age at death was 80.3 (7.5) years in those with, and 84.8 (8.1) in those without, PRBD. The mean USSLB stage[13] across the entire sample was 2.6 with vs 1.0 without PRBD ($p<.0001$.)

PRBD was less frequently present in subjects without LTS, including 4/105 (3.8%) of healthy controls and 42/255 (16.5%) AD, than in subjects with LTS, including 11/46 (23.9%) DLB, and 58/104 (55.8%) PD. Clinician-diagnosed PRBD was present in 6/49 (12.2%) progressive supranuclear palsy (PSP) cases, including 4/6 PSP (66.7%) that had concomitant LTS. PRBD was not present in any of 46 subjects with incidental Lewy body disease (ILBD). Of these, 9 (19.6%) were USSLB Stage I (olfactory only), 21 (45.7%) Stage IIA (brainstem predominant), 8 (17.4%) stage IIB (limbic predominant), 8 (17.4%) stage III (brainstem and limb), none were stage IV (neocortical.)

Final clinicopathological diagnoses of the cases with and without PRBD are summarized in Table 1. The histological presence of LTS (DLB, PD, ILBD, AD plus LTS not meeting criteria for PD or DLB [ADLB], or any other mixed LTS) was found in 278/602 (46.2%) cases overall. Overall, LTS was found in 80/101 (79.2%) of those who had PRBD and 198/501 (39.5%) without ($p <0.001$). Overall sensitivity for predicting LTS by PRBD was 28.8%, specificity 93.5%, positive predictive value (PPV) 79.2%, negative predictive value (NPV) 60.5%.

Among individuals with PRBD, the histological presence of LTS was found in 50.2% with informant-supported MSQ, 36.5% with self-reported MSQ, and 45.1% without MSQ data. With informant-supported MSQ, sensitivity was 53.4%, specificity 84.5%, PPV 77.8%, NPV 64.3%. With self-reported MSQ, sensitivity was 30.4%, specificity 95%, PPV 77.8%, NPV 70.4%. Without MSQ-supported diagnosis sensitivity was 7.3%, specificity 99.4%, PPV 90.9%, NPV 56.7%. The chi-square test (used to compare the sensitivity and specificity

of predicting LTS for these two approaches) was significant for sensitivity and specificity ($p>0.0001$), showing improved sensitivity, but reduced specificity, when clinician diagnosis was supported by MSQ (more so with use of an informant.)

Discussion

We found clinician diagnosis of PRBD to be specific, but not very sensitive, for LTS pathology in our AZSAND population. We found that a large fraction of those with LTS did not have PRBD diagnosed during life (198/278 or 71.2%). While use of the MSQ in diagnosis of PRBD significantly improved sensitivity for detecting LTS to 30.4%, and further to 53.4% with use of an informant (from 7.3% without any MSQ), this still indicates a modest sensitivity of clinician-diagnosed PRBD for predicting the presence of LTS. It is possible that PRBD may not be a stable clinical finding and may regress with disease progression, which could lead to under-reporting if it occurred in the remote past. Therefore, sensitivity of PRBD as a predictor of LTS reported from this study should be viewed as a conservative estimate.

The largest RBD clinicopathological study to date primarily assessed subjects with neurodegenerative disease, and none without RBD were included for comparison. It therefore was not designed to assess both sensitivity and specificity of an RBD diagnosis for detecting LTS. The study found synucleinopathy in 78/80 (98%) of PSG confirmed cases, 58/65 (91%) of PRBD based on clinical history of dream enactment behavior alone, and 23/26 (88%) PRBD by MSQ [1]. Our presented data, in a cohort that was not confined to subjects with RBD or a neurodegenerative disease, found LTS to be less common in subjects with PRBD; only 79% had this at autopsy. The majority of AZSAND autopsied subjects are initially recruited as community-dwelling volunteers with additional recruitment efforts specifically directed at subjects with olfactory dysfunction, dementia or Parkinson’s disease; in the prior study most autopsied subjects were recruited at tertiary care centers with a special interest in DLB, PD and/or RBD [1]. Our findings suggest that, when considering a broader and less selected population, the presence of PRBD has a lower PPV for LTS (79.2%) than that previously reported for a strictly tertiary care setting (91%.)

We found subjects with PRBD were more likely to be male, more likely to have underlying synuclein pathology, had a higher USSLB stage, and died an average of 5 years earlier than those without PRBD (Table 1.) This was true even after excluding individuals without clinical manifestations of brain disease. RBD may thus have negative prognostic survival implications. This has been previously suggested in PD, where RBD has been associated with a more malignant phenotype with earlier disease presentation [15,16] and increased overall synuclein deposition [17]. This is further supported by a previous study revealing DLB subjects with PRBD had a shorter duration of dementia prior to death (mean, 8 vs 10 years) [14]. Given its moderately high PPV for predicting presence of LTS, PRBD may also predict a more aggressive disease course in AD. While not reporting on RBD, a study using National Alzheimer Coordinating Center data found that mixed ADLB patients died an average of 2 years earlier than those with pure AD [18]. However; additional tests are needed to improve upon the modest sensitivity of MSQ in predicting (and prospectively studying) ADLB pathology pre-mortem.

There are limitations to our study. We did not use PSG confirmation to secure a definite RBD diagnosis in our population. However; we used a detailed history (supplemented, where available, by a validated instrument) to support its probable diagnosis, thus reflecting real-world clinical practice (where PSG is not routinely obtained specifically to assess for RBD.) AZSAND was historically designed for community-based enrollment of normally aging and diseased individuals as well as neurologist-referred patients with clinically suspected AD, DLB or PD. Controls with olfactory dysfunction (a PD risk factor)[19] were preferentially enrolled. The 34.4% prevalence of RBD among DLB subjects in our sample (where many were enrolled with an AD clinical diagnosis but found at autopsy to have both AD and DLB) was lower that that described in other autopsy research, where RBD was present in 78.9% of cases meeting established clinical criteria for DLB [14]. Therefore, its findings may not be broadly generalizable to either purely community-based or purely tertiary referral populations that may have differing population structures and/or clinical disease phenotypes. The average age at autopsy in our study participants was relatively high. Our subjects' mean age at death was 85, whereas that in the prior clinicopathological correlation study on RBD was 75 [1]. As a result, the neuropathology in our study subjects may be more heterogeneous than might be found in a younger population (although even AZSAND subjects in their 50s through 70s have considerable heterogeneity)[20] and our subjects might have greater than average longevity. It is possible that our study may be limited by participation bias (volunteer bias), which is associated with a higher socioeconomic status and may be motivated in part by factors such as a subjective sense of impending neurological disease or a family history of neurological disease [10]. Lastly, in the case of those with PRBD but no evidence of LTS, this may be due to sampling parameters at autopsy. When surveying for LTS in the brain we review less than 1% of the brain, making it a possibility that LTS may have been overlooked.

Our study was not able to show any sensitivity of the MSQ for predicting ILBD (with 0/46 ILBD subjects having PRBD), even though fewer than 20% of cases were restricted to the olfactory bulb (USSLB stage I.) This is at first glance surprising, given a wealth of evidence suggesting that both idiopathic RBD (iRBD) and ILBD may be prodromal synucleinopathies [21,22,5,23–25,2]. It might be explained by the advanced age of our ILBD subjects (it may be that the great majority of PRBD subjects will have phenoconverted before their 80s.) It is also possible that ILBD subjects without RBD are somehow resistant to manifesting symptoms. Another alternative explanation is that iRBD is present in a smaller subset of ILBD, which appears likely as ILBD is present in up to 30% of elderly individuals [26] while the prevalence estimates for RBD range from 1.2% (PSG confirmed iRBD) to 13% (PRBD in an elderly community sample.)[27–30] Prospective autopsy research in well-characterized iRBD participants is needed to confirm whether iRBD cases follow typical PD-like pathological stages (starting with LB pathology impacting lower brainstem tracts crucial to REM atonia) or are just as likely to progress along the limbic-predominant pathway [13,31]. More importantly, such work is critical for understanding how common iRBD is in the general population, how often it leads to neurodegenerative disease and the neuroanatomical basis of its distinctive clinical appearance.

Because of its low sensitivity, MSQ supported clinical diagnosis of PRBD alone does not appear sufficient to predict LTS. However; presence of PRBD overall had moderately high

predictive value for presence of LTS- and a negative PRBD diagnosis was also moderately specific for predicting absence of LTS (but highly specific where caregiver-completed MSQ was available). When considered in the context of all available clinical and biomarker information, clinician assessment for PRBD appears useful in guiding differential diagnosis of neurodegenerative disease.

Acknowledgements:

We thank our donors and their families for their contributions of tissue, time and effort to this work.

Funding Sources: This study was funded by the National Institute of Neurological Disorders and Stroke (U24 NS072026 National Brain and Tissue Resource for Parkinson's Disease and Related Disorders), the National Institute on Aging (P30 AG19610 Arizona Alzheimer's Disease Core Center), the Arizona Department of Health Services (contract 211002, Arizona Alzheimer's Research Center), the Arizona Biomedical Research Commission (contracts 4001, 0011, 05–901 and 1001 to the Arizona Parkinson's Disease Consortium), the Michael J. Fox Foundation for Parkinson's Research, the Arizona Alzheimer's Consortium and Mayo Clinic Foundation.

Disclosures:

DRS received research support from the Acorda, Arizona Alzheimer's Consortium, Axovant, Biogen, Intec, Teva, Neurocrine, Michael J Fox Foundation, and NIH; consultant fees from Eli Lilly, Teva, Lundbeck and Weston Brain Institute; speaker fees from Acadia, the Arizona Psychiatric Society, Lundbeck, Teva and the Tourette Association of America.

CHA has received research funding from the Michael J. Fox Foundation, NIH, US Department of Defense, and the Arizona Biomedical Research Foundation, and has received consulting fees from Acadia, Acorda, Cynapsus, Jazz, Lundbeck, Merz, Minerva, Neurocrine, and Sunovion

NZ receives research support from the Arizona Alzheimer's Consortium and NIH.

JGH: received research grant funding for this project from the NIH.

GS: receives research support from Arizona Biomedical Research Commission

BND: has received funding support from grants from the National Institutes of Health, as well as the CurePSP foundation, the Alzheimer's Association, the Henry M. Jackson Foundation, and Daiichi Sankyo Co., Ltd.

HS: received research support from Cynapsus/Sunovion, Axovant, Impax, US World Meds, Michael J. Fox Foundation and the NIH

RS: no disclosures

JC: receives research support from MJFF and Pfizer. RS receives research support from NIH

MNS: receives consulting fees from Axovant, Biogen, Grifols, Humana, Lilly, Sanofi, vTv Therapeutics; research support from AstraZeneca, Avid Pharmaceuticals, Aovant, Genentech, Lilly, Merk, Pfizer, Roche Diagnostics, vTv Therapeutics, Piramal Imaging; and owns stock in Brain Health, Muses Labs, and Versanum

CMB: receives grant support from the Arizona Alzheimer's Consortium, National Institutes of health, MJFF. Research support from Axovant, Biogen, Lilly, Avid, Genentech, AstraZeneca, Merck, Pfizer, Roche, Takeda, Biotie, Neurocrine, Navidea, Novartis, Suven, Abbvie, USC-ALZ Association, and Navidea.

ED-D: no disclosures

SHM: receives consulting fees from Abbvie, Medtronic and Adamas. Research support from Jazz Pharmaceuticals, Pharma 2B, Eli Lily and Arizona Biomedical research Consortium (ABRC)

LS: no disclosures

EZ: receives research support from Eli Lilly, Biogen, Pfizer, Merk, and NIH

TGB: receives grant support from the the Arizona Alzheimer's Consortium, National Institutes of Health and MJFF, performs contracted research for Navidea Biopharamaceuticals and Avid Radiopharmaceuticals, serves as a paid consultant with Genentech, GSK, Roche and Ventana.

References:

1. Boeve BF, Silber MH, Ferman TJ, Lin SC, Benarroch EE, Schmeichel AM et al. (2013) Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med 14:754–762. 10.1016/j.sleep.2012.10.015 [PubMed: 23474058]
2. Iranzo A, Fernandez-Arcos A, Tolosa E, Serradell M, Molinuevo JL, Valldeoriola F et al. (2014) Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One 9:e89741 10.1371/journal.pone.0089741 [PubMed: 24587002]
3. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J (2009) Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology 72:1296–1300. 10.1212/01.wnl.0000340980.19702.6e [PubMed: 19109537]
4. Boeve BF, Silber MH, Parisi JE, Dickson D,W, Ferman TJ, Benarroch EE et al. (2003) Synuclein pathology and REM sleep behavior disorder plus dementia or parkinsonism. Neurology 61:40–45 [PubMed: 12847154]
5. Schenck CH, Boeve BF, Mahowald MW (2013) Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med 14:744–748. 10.1016/j.sleep.2012.10.009 [PubMed: 23347909]
6. International Classification of Sleep Disorders- Third Edition (2014). American Academy of Sleep Medicine, Darien, IL
7. Boeve BF, Molano JR, Ferman TJ, Lin SC, Bieniek K, Tippmann-Peikert M et al. (2013) Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in a community-based sample. J Clin Sleep Med 9:475–480. 10.5664/jcsm.2670 [PubMed: 23674939]
8. Boeve BF, Molano JR, Ferman TJ, Smith GE, Lin SC, Bieniek K et al. (2011) Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. Sleep Med 12:445–453. 10.1016/j.sleep.2010.12.009 [PubMed: 21349763]
9. Adler CH, Hentz JG, Shill HA, Sabbagh MN, Driver-Dunckley E, Evidente VG et al. (2011) Probable RBD is increased in Parkinson's disease but not in essential tremor or restless legs syndrome. Parkinsonism Relat Disord 17:456–458. 10.1016/j.parkreldis.2011.03.007 [PubMed: 21482171]
10. Beach TG, Adler CH, Sue LI, Serrano G, Shill HA, Walker DG et al. (2015) Arizona Study of Aging and Neurodegenerative Disorders and Brain and Body Donation Program. Neuropathology 35:354–389. 10.1111/neup.12189 [PubMed: 25619230]
11. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease (1997). Neurobiol Aging 18:S1–2 [PubMed: 9330978]
12. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H et al. (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65:1863–1872 [PubMed: 16237129]
13. Beach TG, Adler CH, Lue L, Sue LI, Bachalakuri J, Henry-Watson J et al. (2009) Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. Acta Neuropathol 117:613–634. 10.1007/s00401-009-0538-8 [PubMed: 19399512]
14. Dugger BN, Boeve BF, Murray ME, Parisi JE, Fujishiro H, Dickson DW et al. (2012) Rapid eye movement sleep behavior disorder and subtypes in autopsy-confirmed dementia with Lewy bodies. Mov Disord 27:72–78. 10.1002/mds.24003 [PubMed: 22038951]
15. Fereshtehnejad SM, Romenets SR, Anang JB, Latreille V, Gagnon JF, Postuma RB (2015) New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression: A Prospective Cohort

Comparison With Other Phenotypes. JAMA neurology 72:863–873. 10.1001/jamaneurol.2015.0703 [PubMed: 26076039]

16. Nomura T, Inoue Y, Kagimura T, Nakashima K (2013) Clinical significance of REM sleep behavior disorder in Parkinson's disease. Sleep Med 14:131–135. 10.1016/j.sleep.2012.10.011 [PubMed: 23218532]
17. Postuma RB, Adler CH, Dugger BN, Hentz JG, Shill HA, Driver-Dunckley E et al. (2015) REM sleep behavior disorder and neuropathology in Parkinson's disease. Mov Disord 30:1413–1417. 10.1002/mds.26347 [PubMed: 26265105]
18. Chung EJ, Babulal GM, Monsell SE, Cairns NJ, Roe CM, Morris JC (2015) Clinical Features of Alzheimer Disease With and Without Lewy Bodies. JAMA neurology 72:789–796. 10.1001/jamaneurol.2015.0606 [PubMed: 25985321]
19. Ross GW, Abbott RD, Petrovitch H, Tanner CM, Davis DG, Nelson JC et al. (2006) Association of olfactory dysfunction with incidental Lewy bodies. Mov Disord 21:2062–2067 [PubMed: 16991138]
20. Caselli RJ, Beach TG, Knopman DS, Graff-Radford NR (2017) Alzheimer Disease: Scientific Breakthroughs and Translational Challenges. Mayo Clinic proceedings 92:978–994. 10.1016/j.mayocp.2017.02.011 [PubMed: 28578785]
21. Adler CH, Connor DJ, Hentz JG, Sabbagh MN, Caviness JN, Shill HA et al. (2010) Incidental Lewy body disease: clinical comparison to a control cohort. Mov Disord 25:642–646. 10.1002/mds.22971 [PubMed: 20175211]
22. Frigerio R, Fujishiro H, Ahn TB, Josephs KA, Maraganore DM, DelleDonne A et al. (2011) Incidental Lewy body disease: do some cases represent a preclinical stage of dementia with Lewy bodies? Neurobiol Aging 32:857–863. 10.1016/j.neurobiolaging.2009.05.019 [PubMed: 19560232]
23. Fernandez-Arcos A, Iranzo A, Serradell M, Gaig C, Santamaria J (2016) The Clinical Phenotype of Idiopathic Rapid Eye Movement Sleep Behavior Disorder at Presentation: A Study in 203 Consecutive Patients. Sleep 39:121–132. 10.5665/sleep.5332 [PubMed: 26940460]
24. Driver-Dunckley E, Adler CH, Hentz JG, Dugger BN, Shill HA, Caviness JN et al. Olfactory dysfunction in incidental Lewy body disease and Parkinson's disease. Parkinsonism & Related Disorders 20:1260–1262. 10.1016/j.parkreldis.2014.08.006
25. Iacono D, Geraci-Erck M, Rabin ML, Adler CH, Serrano G, Beach TG et al. (2015) Parkinson disease and incidental Lewy body disease: Just a question of time? Neurology 85:1670–1679. 10.1212/wnl.0000000000002102 [PubMed: 26468408]
26. Jellinger KA (2004) Lewy body-related alpha-synucleinopathy in the aged human brain. J Neural Transm (Vienna) 111:1219–1235. 10.1007/s00702-004-0138-7 [PubMed: 15480835]
27. Dauvilliers Y, Postuma RB, Ferini-Strambi L, Arnulf I, Hogl B, Manni R et al. (2013) Family history of idiopathic REM behavior disorder: a multicenter case-control study. Neurology 80:2233–2235. 10.1212/WNL.0b013e318296e967 [PubMed: 23658378]
28. Wong JC, Li J, Pavlova M, Chen S, Wu A, Wu S et al. (2016) Risk factors for probable REM sleep behavior disorder: A community-based study. Neurology 86:1306–1312. 10.1212/WNL.0000000000002414 [PubMed: 26819459]
29. Mahlknecht P, Iranzo A, Hogl B, Frauscher B, Muller C, Santamaria J et al. (2015) Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD. Neurology 84:654–658. 10.1212/WNL.0000000000001265 [PubMed: 25609758]
30. St Louis EK, Boeve AR, Boeve BF (2017) REMSleep Behavior Disorder in Parkinson's Disease and Other Synucleinopathies. Movement Disorders 32:645–658. 10.1002/mds.27018 [PubMed: 28513079]
31. Adler CH, Beach TG (2016) Neuropathological basis of nonmotor manifestations of Parkinson's disease. Mov Disord 31:1114–1119. 10.1002/mds.26605 [PubMed: 27030013]

Table 1.

Demographics and Diagnosis with and without pRBD by informant-completed MSQ

	No (N=174)	Yes (N=70)	Total (N=244)	p value
Death Age (y)				
Mean (SD)	85.8 (7.7)	79.9 (7.3)	84.1 (8.0)	<0.0001
Median	86.0	80.0	84.0	
Range	(44.0–106.0)	(62.0–100.0)	(44.0–106.0)	
Male	110 (66.7%)	55 (33.3%)	165 (67.6%)	0.0204
Female	64 (81.0%)	15 (19.0%)	79 (32.4%)	
MSQ Interval (y)	0.6 (2.5)	1.0 (0.8)	0.7 (2.2)	
Mean (SD)	0.9	0.7	0.9	0.0798
Median	(−10.1–6.6)	(0.0–3.9)	(−10.1–6.6)	
Range	40 (95.2%)	2 (4.8%)	42 (17.2%)	
Final Diagnosis				
Control	40 (95.2%)	2 (4.8%)	42 (17.2%)	0.0001
AD	70 (69.3%)	31 (30.7%)	101 (41.4%)	0.5607
AD with LB pathology	30 (51.7%)	28 (48.3%)	58 (23.8%)	
AD without LB pathology	34 (79.1%)	9 (20.9%)	43 (17.6%)	
VaD	19 (86.4%)	3 (13.6%)	22 (9.0%)	0.1380
Dementia NOS	0 (0.0%)	2 (100.0%)	2 (0.8%)	0.0815
FTD	1 (100.0%)	0 (0.0%)	1 (0.4%)	1.0000
Tauopathy NOS	16 (72.7%)	6 (27.3%)	22 (9.0%)	0.8777
HS	1 (100.0%)	0 (0.0%)	1 (0.4%)	1.0000
AG	21 (80.8%)	5 (19.2%)	26 (10.7%)	0.2593
DLB	14 (63.6%)	8 (36.4%)	22 (9.0%)	0.4040
LB	19 (70.4%)	8 (29.6%)	27 (11.1%)	0.9087
ILBD	19 (100.0%)	0 (0.0%)	19 (7.8%)	0.0040
PD	18 (32.7%)	37 (67.3%)	55 (22.5%)	<0.0001
Parkinsonism NOS	7 (100.0%)	2 (0.0%)	9 (3.7%)	0.5276
IPSP	1 (100.0%)	0 (0.0%)	1 (0.6%)	0.3443
MSA	0 (0.0%)	1 (100.0%)	1 (0.4%)	1.0000
FD PSP	11 (6.3%)	6 (2.5%)	11 (4.5%)	0.5528
PSP with LB pathology	2 (33.3%)	4 (66.7%)	6 (2.5%)	
PSP without LB pathology	9 (81.8%)	2 (18.2%)	11 (4.5%)	
FD CBD	2 (66.7%)	1 (33.3%)	3 (1.2%)	1.0000
FD NFTD	0 (0.0%)	2 (100.0%)	2 (1.6%)	0.1167
FD Other Type				0.4643
ALS	1 (100.0%)	0 (0.0%)	1 (12.5%)	
MS	0 (0.0%)	1 (100.0%)	1 (12.5%)	
Brain Cancer	5 (83.3%)	1 (16.7%)	6 (75.0%)	

AD: Alzheimer disease; CBD: corticobasal degeneration; DLB: dementia with Lewy bodies; AG: argyrophylic grain disease; ALS: amyotrophic lateral sclerosis; HS: hippocampal sclerosis; ILBD: incidental Lewy body disease; IPSP: incidential PSP pathology without symptoms; FTD:

Frontotemporal dementia; LB: Lewy body disease not meeting clinical diagnostic criteria; MSA: multiple system atrophy; MSQ Interval: Interval between last MSQ and death; NFTD: neurofibrillary tangle predominant dementia; PSP: progressive supranuclear palsy; VaD: vascular dementia