Clinical Autonomic Research (2023) 33:387–389
https://doi.org/10.1007/s10286-023-00968-4

Recent updates in autonomic research: orthostatic hypotension and cognitive function in Parkinson disease and multiple system atrophy, the skin as a window into synuclein pathology, and *RFC1* repeat expansions in hereditary sensory autonomic neuropathies

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Received: 15 July 2023 / Accepted: 15 July 2023 / Published online: 26 July 2023

Keywords Autonomic · Multiple system atrophy · Parkinson disease · Orthostatic hypotension · Cognition · Genetic · Skin biopsy · Neuropathy

Orthostatic hypotension and cognitive function in Parkinson disease and multiple system atrophy

Orthostatic hypotension (OH) reflects insufficient hemodynamic adjustment to postural changes, which may exceed the threshold of cerebral autoregulation resulting in decreased cerebral perfusion during orthostatic stress. Cognitive testing during upright position in Parkinson disease (PD) patients with OH demonstrated transient impairment in cognition with more pronounced deficits in executive function, memory, and visuospatial domains [1]. Patients who experience repeated bouts of OH may be predisposed to chronic brain hypoxia leading to progressive cognitive decline and dementia, especially in the setting of synergistic neurodegenerative processes. Multiple studies have shown the association between OH and dementia as well as cognitive impairment progression to dementia, even when OH was asymptomatic [2, 3].

OH is one of the main non-motor features of synucleinopathies, found in approximately 30% of individuals with PD [4] and 70% of individuals with multiple system atrophy (MSA) [5]. In an article published in *Neurology*, Ruiz Barrio et al. retrospectively reviewed the medical records of consecutive neuropathology-confirmed patients with PD and MSA and evaluated the association between neurogenic OH and dementia/cognitive impairment risk [6]. Multivariable-adjusted regression models from 132 PD and 137 MSA demonstrated that early OH independently increased dementia risk in PD by 14% per year and cognitive impairment risk in MSA by 41% per year. The severity of OH symptoms and concomitant supine hypertension were not associated with any significant change in dementia/cognitive impairment risk. Clinical–pathological correlation showed that early OH was not associated with increased alpha-synuclein, beta-amyloid, tau, or cerebrovascular pathologies. No significant differences in cortical Lewy pathology were found between subgroups suggesting that the association between OH and dementia may not be due to a shared neuroanatomical basis.

Similar to prior studies [7–9], the study by Ruiz Barrio et al. demonstrates the association between OH and dementia in PD. As neurogenic OH can be present in the early stages of PD, OH could be a potential intervention target to modify dementia risk factors in PD patients. Whether improving brain perfusion by treating OH can reduce dementia requires further study. PD patients who experience symptoms from OH should be identified and treated nevertheless. Screening for early detection of OH in PD should also be considered regardless of symptoms of orthostatic intolerance.

Although OH has been linked to dementia in synucleinopathies, there are likely many other factors contributing to cognitive decline. These factors may explain why MSA patients paradoxically have lower rates of cognitive impairment despite more frequent and severe OH. MSA patients have shorter survival compared to PD and perhaps less cumulative damage from OH-related hypoxia. However, this would not explain the case of infrequent dementia in

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patients with pure autonomic failure who frequently have a long duration of exposure to severe OH.

The skin, a window into synuclein pathology

Although synucleinopathies like PD and MSA continue to be diagnosed mainly on clinical criteria, the hunt for reliable biomarkers to improve diagnostic accuracy is advancing. There is particular interest in accessible and minimally invasive methods, such as skin biopsies. Detection of phosphorylated α-synuclein (P-SYN) in skin nerve fibers shows promising sensitivity and specificity in differentiating synucleinopathies from healthy individuals and non-synuclein pathologies such as tauopathies [10]. The accuracy of this technique in separating different synucleinopathies from one another has been explored more recently.

A study published in the April 2023 issue of *Neurology* by Gibbons et al. set out to use pathological features on skin biopsies to distinguish MSA from PD [11]. The authors conducted a prospective, three-site, single-visit cohort study that recruited 31 patients with probable MSA, 54 patients with PD, and 24 matched controls. All patients underwent neurological examination, disease-specific rating scales, autonomic testing, and a punch skin biopsy at three sites (posterior cervical region, proximal and distal thigh). Skin samples were examined for P-SYN (only deposits colocalizing with stained nerve fibers) as well as for intraepidermal, sweat gland, and pilomotor nerve fiber densities.

This study reports several interesting findings. First, P-SYN was shown again to be specific for synucleinopathies since none was detected in healthy controls. Second, alpha-synuclein behaves differently in MSA and PD in the periphery: not only was there significantly higher P-SYN deposition in participants with MSA, but the distribution was also a distinguishing characteristic, with MSA having a widespread distribution and PD showing a pattern of greater deposition in the cervical region, decreasing distally. Combining specific thresholds of a distribution coefficient score and total P-SYN deposition resulted in 96.8% sensitivity and 98.1% specificity in distinguishing MSA from PD.

The authors also found a mild small fiber sensory and autonomic neuropathy in patients with PD that was not seen in MSA patients and controls. The gradient of nerve fiber loss seen in PD raises the question of whether the gradient of P-SYN in this population was a direct consequence of peripheral neuropathy. Patients with comorbidities that cause peripheral neuropathy were excluded from this study, a limitation to its external validity. Considering the real-world prevalence of these conditions, inclusion of patients with neuropathy in future work will be important to ensure this method remains accurate in discriminating between the different synucleinopathy groups as well as controls.

There is a clear trade-off of including patients with relatively longer disease duration. This allowed increased certainty in the clinical diagnosis since distinguishing MSA and PD is most challenging early in the disease course. However, demonstrating that the described cutaneous patterns remain sensitive and specific at a stage of the disease where the clinical picture is still nebulous will be crucial to prove its utility. In addition, since diagnostic accuracy was determined based on clinically established criteria, validation using autopsy studies will also be important; as pointed out by the authors, clinical diagnostic accuracy is imperfect, even beyond early disease [12].

The role that detecting P-SYN on skin biopsies will play in clinical practice is still unclear, and future studies with larger sample sizes are needed. One such study, the Synuclein-One study, has already completed enrollment and will present cutaneous P-SYN findings for hundreds of participants including PD, MSA, dementia with Lewy bodies, pure autonomic failure, and healthy controls [13]. Based on the data presented at the 2023 AAN Annual Meeting, the Syn-One test is reportedly highly sensitive and specific in detecting P-SYN across these pathologies, and we look forward to this study's discussion of specific pathological features of each synucleinopathy.

RFC1 repeat expansions: a frequent cause of hereditary sensory and autonomic neuropathies

Hereditary sensory and autonomic neuropathies (HSAN) is a clinically and genetically heterogeneous group of inherited neuropathies characterized by predominant loss of sensation, pain, and autonomic dysfunction [14]. The number of genes associated with HSAN phenotype has been growing in recent years; however, the majority of HSAN patients are still left with unidentified genetic causes after whole exome sequencing (WES).

In an article published in the European Journal of Neurology, *Beijer* et al. performed a repeat-primed PCR to investigate the presence of replication factor C subunit 1 (*RFC1*) repeat expansions in a cohort of WES-negative HSAN patients [15]. Among 12 HSAN families (22 Caucasian individuals) who also presented with chronic cough, 9 families (75%) had biallelic *RFC1* expansions of the AAGGG motif. Patients with biallelic *RFC1* expansions presented more consistently with autonomic and positive sensory symptoms with more severe sensory ataxia when compared to the *RFC1*-negative group. Cerebellar ataxia was a common feature and exclusively present in those with *RFC1* expansion in their cohort.

RFC1 repeat expansions are known to associate with cerebellar ataxia, neuropathy, vestibular areflexia syndrome

(CANVAS) as well as other phenotypic spectrum including sensory neuropathy/neuronopathy, autonomic dysfunction, parkinsonism, and chronic cough [16]. Because of its intronic location, pathogenic *RFC1* expansion cannot be detected by sequence-based multigene panels or WES. Given the surprisingly high frequency of *RFC1* expansion among HSAN patients demonstrated in this study and another study from Japan [15, 17], genetic screening to look for the *RFC1* repeat expansion by PCR methodology should be included when working up patients with HSAN especially those with chronic cough.

The phenotypic variability in patients with biallelic expansions in RFC1 makes the diagnosis very challenging. Cerebellar ataxia, when present, can help distinguish patients with RFC1 expansions from other HSAN patients. On the other hand, the combination of cerebellar ataxia, Parkinsonism, and autonomic dysfunction can mimic multiple system atrophy, cerebellar type (MSA-C). The autonomic impairment of patients with *RFC1* expansion is typically mild but can sometimes progress to severe widespread autonomic failure with mixed pre- and post-ganglionic involvement similar to MSA [18]. That being said, no patients with pathogenic *RFC1* expansions were identified in a cohort of 336 pathologically confirmed MSA suggesting that RFC1 expansion is not a cause of MSA although *RFC1*-related disorders and MSA have overlapping phenotypes [19]. Hence, *RFC1* expansion should not be routinely tested in all MSA patients but should come to mind when evaluating MSA-like patients with atypical features such as sensory neuropathy and chronic cough.

Funding No funding to declare.

Data availability Not applicable.

Declarations

Conflict of interest The author(s) declare that they have no conflict of interest.

References

1. Centi J, Freeman R, Gibbons CH, Neargarder S, Canova AO, Cronin-Golomb A (2017) Effects of orthostatic hypotension on cognition in Parkinson disease. Neurology 88(1):17–24. https://doi.org/10.1212/wnl.0000000000003452
2. Ou YN, Tan CC, Shen XN, Xu W, Hou XH, Dong Q et al (2020) Blood pressure and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 209 prospective studies. Hypertension 76(1):217–225. https://doi.org/10.1161/hypertensionaha.120.14993
3. Xia X, Wang R, Vetrano DL, Grande G, Laukka EJ, Ding M et al (2021) From normal cognition to cognitive impairment and dementia: impact of orthostatic hypotension. Hypertension 78(3):769–778. https://doi.org/10.1161/hypertensionaha.121.17454
4. Velseboer DC, de Haan RJ, Wieling W, Goldstein DS, de Bie RM (2011) Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis. Parkinsonism Relat Disord 17(10):724–729. https://doi.org/10.1016/j.parkreldis.2011.04.016
5. Wenning GK, Ben Shlomo Y, Magalhães M, Daniel SE, Quinn NP (1994) Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. Brain 117(Pt 4):835–845. https://doi.org/10.1093/brain/117.4.835
6. Ruiz Barrio I, Miki Y, Jaunmuktane ZT, Warner T, De Pablo-Fernandez E (2023) Association between orthostatic hypotension and dementia in patients with Parkinson disease and multiple system atrophy. Neurology 100(10):e998–e1008. https://doi.org/10.1212/wnl.0000000000201659
7. Loureiro D, Bilbao R, Bordet S, Grasso L, Otero-Losada M, Capani F et al (2023) A systematic review and meta-analysis on the association between orthostatic hypotension and mild cognitive impairment and dementia in Parkinson's disease. Neurol Sci 44(4):1211–1222. https://doi.org/10.1007/s10072-022-06537-3
8. McDonald C, Newton JL, Burn DJ (2016) Orthostatic hypotension and cognitive impairment in Parkinson's disease: causation or association? Mov Disord 31(7):937–946. https://doi.org/10.1002/mds.26632
9. Udow SJ, Robertson AD, MacIntosh BJ, Espay AJ, Rowe JB, Lang AE et al (2016) "Under pressure": is there a link between orthostatic hypotension and cognitive impairment in α-synucleinopathies? J Neurol Neurosurg Psychiatry 87(12):1311–1321. https://doi.org/10.1136/jnnp-2016-314123
10. Donadio V (2019) Skin nerve α-synuclein deposits in Parkinson's disease and other synucleinopathies: a review. Clin Auton Res 29(6):577–585. https://doi.org/10.1007/s10286-018-0581-4
11. Gibbons C, Wang N, Rajan S, Kern D, Palma JA, Kaufmann H et al (2023) Cutaneous α-synuclein signatures in patients with multiple system atrophy and Parkinson disease. Neurology 100(15):e1529–e1539. https://doi.org/10.1212/wnl.0000000000206772
12. Adler CH, Beach TG, Hentz JG, Shill HA, Caviness JN, Driver-Dunckley E et al (2014) Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. Neurology 83(5):406–412. https://doi.org/10.1212/wnl.0000000000000641
13. Gibbons CH, Freeman R, Bellaire B, Adler CH, Moore D, Levine T (2022) Synuclein-one study: skin biopsy detection of phosphorylated α-synuclein for diagnosis of synucleinopathies. Biomark Med 16(7):499–509. https://doi.org/10.2217/bmm-2021-0646
14. Rotthier A, Baets J, De Vriendt E, Jacobs A, Auer-Grumbach M, Lévy N et al (2009) Genes for hereditary sensory and autonomic neuropathies: a genotype-phenotype correlation. Brain 132(Pt 10):2699–2711. https://doi.org/10.1093/brain/awp198
15. Beijer D, Dohrn MF, De Winter J, Fazal S, Cortese A, Stojkovic T et al (2022) RFC1 repeat expansions: a recurrent cause of sensory and autonomic neuropathy with cough and ataxia. Eur J Neurol 29(7):2156–2161. https://doi.org/10.1111/ene.15310
16. Cortese A, Reilly MM, Houlden H (2020) RFC1 CANVAS/Spectrum Disorder. In: Adam MP, Mirzaa GM, Pagon RA, et al (eds) GeneReviews® [Internet]. University of Washington, Seattle, 1993–2023. https://www.ncbi.nlm.nih.gov/books/NBK564656/
17. Yuan JH, Higuchi Y, Ando M, Matsuura E, Hashiguchi A, Yoshimura A et al (2022) Multi-type RFC1 repeat expansions as the most common cause of hereditary sensory and autonomic neuropathy. Front Neurol 13:986504. https://doi.org/10.3389/fneur.2022.986504
18. Record CJ, Alsukhni RA, Curro R, Kaski D, Rubin JS, Morris HR et al (2022) Severe distinct dysautonomia in RFC1-related disease associated with Parkinsonism. J Peripher Nerv Syst 27(4):311–315. https://doi.org/10.1111/jns.12515
19. Sullivan R, Yau WY, Chelban V, Rossi S, O'Connor E, Wood NW et al (2020) RFC1 intronic repeat expansions absent in pathologically confirmed multiple systems atrophy. Mov Disord 35(7):1277–1279. https://doi.org/10.1002/mds.28074