Clinical implications of delayed orthostatic hypotension

A 10-year follow-up study

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ABSTRACT

Objective: To define the long-term outcome of delayed orthostatic hypotension (OH).

Hypothesis: Delayed OH is an early and milder form of OH that progresses over time.

Methods: We reviewed the medical records of 230 previously reported patients who completed autonomic testing at our center from January 1, 2002, through December 31, 2003. All available information on clinical diagnosis, mortality, medication use, and autonomic testing were extracted and included in the reported outcomes. Standard criteria were used to define OH and delayed OH.

Results: Forty-eight individuals with delayed OH, 42 individuals with OH, and 75 controls had complete follow-up data. Fifty-four percent of individuals with delayed OH progressed to OH. Thirty-one percent of individuals with delayed OH developed an α-synucleinopathy. The 10-year mortality rate in individuals with delayed OH was 29%, in individuals with baseline OH was 64%, and in controls was 9%. The 10-year mortality of individuals who progressed to OH was 50%. Progression to OH was associated with developing an α-synucleinopathy, baseline diabetes, and abnormal baseline autonomic test results.

Conclusion: Delayed OH frequently progresses to OH with a high associated mortality. *Neurology*® 2015;85:1362–1367

GLOSSARY

BP = blood pressure; **DOH** = delayed OH; **E:I** = expiratory to inspiratory; **OH** = orthostatic hypotension.

Orthostatic hypotension (OH) is a reduction in systolic blood pressure (BP) of at least 20 mm Hg or diastolic BP of at least 10 mm Hg within 3 minutes of standing, or a similar fall in BP within 3 minutes of upright tilt-table testing to at least 60°. However, the duration of time necessary to detect a fall in BP that is clinically meaningful may extend beyond 3 minutes. Over 20 years ago, Streeten and Anderson[1] introduced the concept of delayed OH (DOH)—a BP fall on standing or upright tilt-table testing that occurred after the 3-minute cutoff. We extended those findings in a report documenting that DOH occurred with the same frequency as OH in a population of individuals referred for autonomic testing.[2] In addition, DOH was associated with both parasympathetic and sympathetic adrenergic dysfunction, although of less severity than in those individuals with a fall in BP within 3 minutes of standing or tilt-table testing.

DOH is now widely recognized among specialists as a potential cause of orthostatic intolerance and is included in a recent consensus statement on disorders of orthostatic intolerance.[3] However, despite several cross-sectional studies of individuals with DOH, there are no longitudinal data available.[1,2,4] Further, it is not known whether DOH is an early presentation of OH, or whether it is a more benign or nonprogressive form of orthostatic intolerance.

We hypothesized that DOH was an early and milder form of OH. We therefore expected that DOH would progress to OH over time, would be associated with similar underlying disease mechanisms, and would have similar long-term complications. In order to investigate these hypotheses, we reviewed the medical records of all individuals reported in our original DOH study.[2] Here, we present the 10-year follow-up data of the groups described in that study.[2]

Editorial, page 1358

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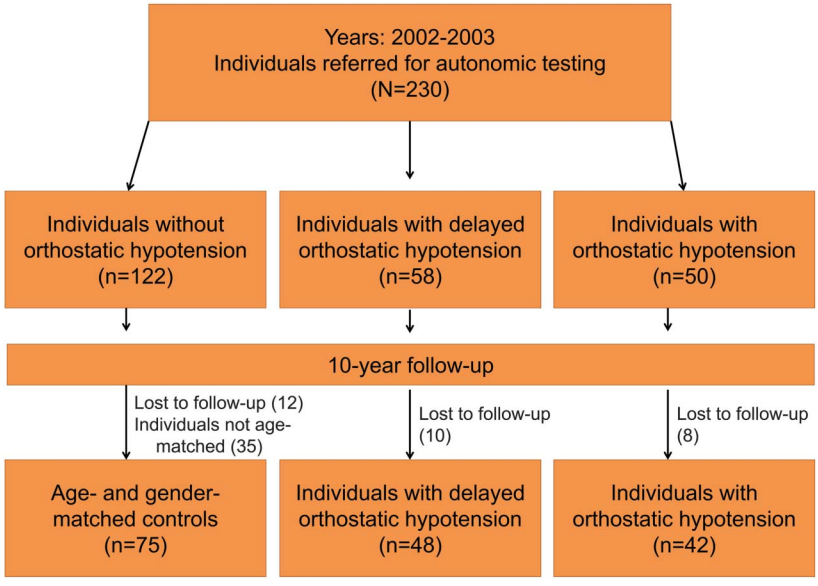
METHODS We reviewed all medical records of the 230 previously reported individuals who completed autonomic testing at our center from January 1, 2002, through December 31, 2003.[2] At the time of their initial evaluation, all individuals had a complete battery of autonomic tests as previously described.[2,5] Briefly, testing was performed in a quiet environment with continuous ECG tracing and beat-to-beat BP response (Finapres, Ohmeda, Englewood, CO) for all tests. Patients rested in a supine position for 20 minutes prior to testing. Parasympathetic function was reported as the heart rate response to paced breathing (6 cycles per minute), described as the average difference in maximum and minimum heart rates and the expiratory to inspiratory (E:I) ratio. A Valsalva maneuver was performed by expiring against a 40 mm Hg pressure for 15 seconds into an open loop system. The Valsalva ratio (a measure of parasympathetic function) and beat-to-beat change in BPs (the drop in phase 2 BP, phase 2 recovery, and phase 4 overshoot) were reported. BPs were measured noninvasively at 1-minute intervals with an automated cuff sphygmomanometer over the right brachial artery (Colin PressMate, Colin Medical, San Antonio, TX) during a 60° head-up tilt for 45 minutes followed by a 10-minute supine rest period. Patients then stood in the upright position for 5 minutes (active stand) with continuous heart rate recording and BPs measured noninvasively at 1-minute intervals. Change in heart rate with standing was quantified by the RR interval at the 30th second divided by the RR interval at the 15th second of standing (the 30:15 ratio). Participants were asked to hold all medications that could impact autonomic function for at least 24 hours prior to testing. All test results are reported as normal or abnormal when compared against age- and sex-specific normative values.

At the time of initial evaluation, all individuals with a fall in systolic BP of ≥20 mm Hg and fall in diastolic BP of ≥10 mm Hg were diagnosed with OH, and any associated symptoms were reported. Those individuals with sustained OH that occurred within 3 minutes were categorized as OH while those individuals developing OH beyond 3 minutes of upright tilt-table testing were categorized as DOH. Only patients with sustained falls in BP were reported to have OH (i.e., transient drops in BP or individuals with neurally mediated syncope were not included).

Figure 1 Study participants



Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram of the participants involved in this study.

In this follow-up study, we reviewed all medical records, test results, and study visits of the 230 individuals reported in the original study through December 31, 2013. A total of 108 in the original study had a fall in BP consistent with OH or DOH. Amongst the 122 individuals without evidence of OH on initial testing, we selected similarly age- and sex-matched participants to serve as control participants (n = 75). All available data on clinical diagnosis, morbidity, mortality, medication use, and additional testing data were extracted and included in the reported outcomes. Cardiac disease among this cohort was defined as individuals with coronary artery disease, ischemic heart disease, congestive heart failure, valvular heart disease, or atrial fibrillation. Follow-up data on OH were obtained by orthostatic vital signs obtained during clinical visits.

Standard protocol approvals, registrations, and patient consents. The protocol was approved by the institutional review board of the Beth Israel Deaconess Medical Center. Data are presented as raw values, mean ± SD, median, and range as appropriate. Autonomic test result data were analyzed using analysis of variance and Student *t* test where applicable. Binary data were analyzed using Fisher exact test or χ^2 test as appropriate. Relationships among variables were determined using linear regression. A p value <0.05 was considered significant. All analyses were done using SPSS 17 (SPSS Inc., Chicago, IL).

RESULTS **Demographic information.** Of the original 108 individuals with OH or DOH described in our initial publication on DOH,[2] 90 had complete follow-up data, and 18 were lost to follow-up. Of those with follow-up data, 42/50 participants had OH and 48/58 participants had DOH in the initial study.

Seventy-five age- and sex-matched controls were selected (see Methods) from the original 122 individuals without OH. Excluded participants included 12 participants with incomplete follow-up data (age 46 ± 8 years) and 35 participants who were not age-matched (all <40 years of age). The mean age of all individuals included in this study at the time of the original testing in 2002 was 59 ± 11 years (49% female). The distribution of participants included in the study is outlined in figure 1 with detailed demographic data by subgroup listed in table 1.

Cohort outcomes. Of the 42 individuals with OH on initial testing, 27 had died (10-year mortality of 64%). Of the 48 with DOH on initial testing, 14 had died (10-year mortality of 29%). Of the 75 age- and sex-matched control participants tested in 2002, 7 had died (10-year mortality of 9%). The initial diagnosis, the follow-up diagnosis, and the mortality rate for each of the specific diseases among the groups is shown in figure 2. The 10-year mortality rates among those individuals diagnosed with a synucleinopathy (Parkinson disease, dementia with Lewy bodies, multiple system atrophy, or pure autonomic failure) were high. All individuals diagnosed with multiple system atrophy had died at the time of follow-up. Among the control group, 5 individuals developed a synucleinopathy. One individual developed Parkinson disease and died

Table 1 Summary of the autonomic testing results from the initial evaluation by group

	Control group	Delayed OH, no progression	Delayed OH, progression to OH	Orthostatic hypotension	*p* Value
No. of patients	75	22	26	42	
Age at diagnosis (2002–2003), y	59 ± 11	45 ± 9	56 ± 13	62 ± 13	<0.05[a]
Female, n (%)	36 (48)	12 (55)	16 (62)	21 (50)	
Mortality rate, n (%)	7 (9)	1 (5)	13 (50)	27 (64)	<0.005[b]
Baseline BP, mm Hg	129/82	131/70 ± 15/9	143/74 ± 28/12	147/76 ± 30/11	<0.05[a]
E:I ratio to deep breathing	1.31 ± 0.11	1.33 ± 0.16	1.18 ± 0.17	1.10 ± 0.11	<0.005[a]
Max-min HR to deep breathing	14 ± 5	16 ± 7	11 ± 9	8 ± 6	<0.01[a]
Valsalva ratio	1.43 ± 0.14	1.45 ± 0.21	1.28 ± 0.19	1.19 ± 0.19	<0.005[a]
Phase II fall during VM	28 ± 10	31 ± 14	38 ± 15	53 ± 19	<0.005[a]
Phase IV overshoot during VM	21 ± 11	16 ± 8	9 ± 6	3 ± 8	<0.005[a]
Mean BP fall during first 3 min of tilt, mm Hg	8/2 ± 6/5	14/8 ± 10/4	16/8 ± 8/6	28/12 ± 12/5	<0.05
Maximum mean BP fall during tilt, mm Hg	10/2 ± 6/6	23/12 ± 12/6	24/12 ± 10/7	34/13 ± 13/6	<0.05[a]
Mean BP fall during active stand, mm Hg	14/7 ± 9/5	20/10 ± 7/8	21/9 ± 10/6	33/17 ± 13/8	<0.05[a]
Stand 30:15 heart rate ratio	1.24 ± 0.08	1.25 ± 0.09	1.12 ± 0.05	1.05 ± 0.04	<0.01[a]

Abbreviations: BP = blood pressure; E:I = expiratory:inspiratory; max-min = maximum to minimum; HR = heart rate; OH = orthostatic hypotension; VM = Valsalva maneuver.
Values are mean ± SD unless noted otherwise.
[a] *p* Value for analysis of variance.
[b] *p* Value for 4 × 2 contingency table.

(figure 2). A summary of mortality data are noted in a Kaplan-Meier curve (figure 3).

Diabetes was present in 57 individuals; 32 in the control group and 25 in the orthostatic or DOH groups. A diagnosis of diabetes and some form of OH on initial testing conveyed a 64% 10-year mortality rate (there was a 69% mortality among those with OH on initial testing and a 44% mortality among those with DOH on initial testing). Among those with diabetes and DOH on initial testing, the mortality rate was 80% among those that progressed to OH, and was 25% among those with DOH that did not progress to OH (figure 2). Diabetes alone (no OH or DOH) conveyed a 13% 10-year mortality rate ($p < 0.001$, Fisher exact test).

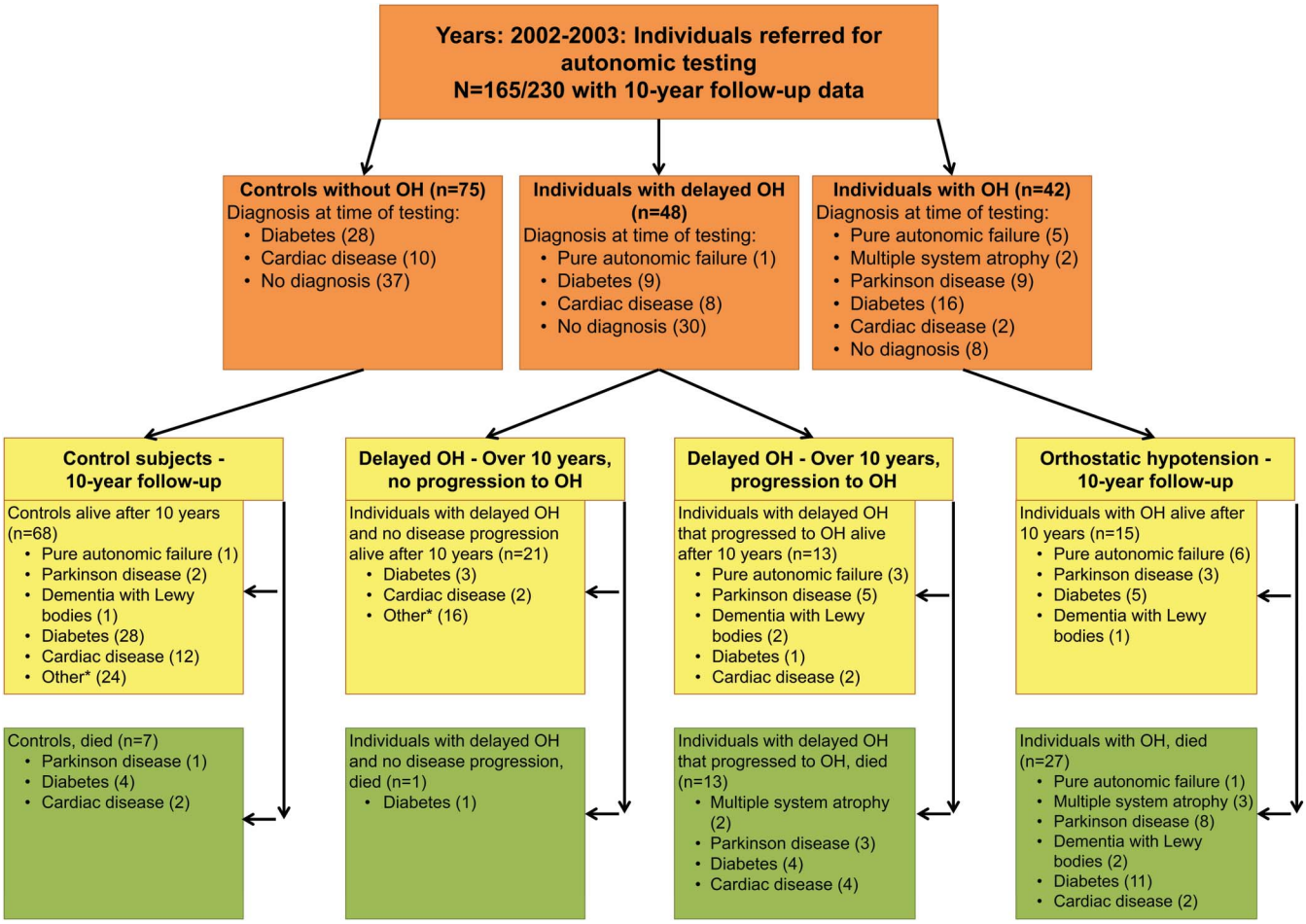
Among those individuals with DOH on initial testing, 26/48 developed OH during the follow-up period. Fifteen of the 26 individuals with DOH who developed OH were diagnosed with synucleinopathies. Only 1 individual carried a synucleinopathy diagnosis at the time of original testing (pure autonomic failure); the remaining 14 individuals developed Parkinson disease, dementia with Lewy bodies, multiple system atrophy, or pure autonomic failure after the diagnosis of DOH. The majority of the 22/48 individuals who did not progress to OH were taking vasoactive medications. In addition, on initial autonomic testing these individuals with DOH who did not progress to OH had little evidence of parasympathetic dysfunction. A summary of the autonomic testing results from the initial evaluation by group is described in table 1.

Autonomic function by cohort. In addition to the absolute values of the test results shown in table 1, we report the number of abnormal values by test when compared against our age- and sex-derived normative values in table 2. Individuals with DOH who did not progress to OH had largely normal parasympathetic function, while those individuals with DOH who did progress to OH had several abnormal tests of parasympathetic function. The differences between groups were highly significant ($p < 0.0001$, Fisher exact test, table 2).

Medication usage. Although medications that could impact autonomic function were held prior to testing, some medications have half-lives of sufficient duration to influence autonomic function despite discontinuation. Those taking medications with potential autonomic nervous system effects included 9% of controls, 68% of individuals with DOH who did not progress to OH, 31% of individuals with DOH who did progress to OH, and 31% of those with OH. The medications included diuretics, β-blockers, tricyclic antidepressants and vasodilating antihypertensive medications.

DISCUSSION DOH is defined as a fall in BP that fulfills criteria for OH but occurs after 3 minutes of standing or upright tilt.[3] In this article, we report the first long-term follow-up data of individuals

Figure 2 Summary of outcomes



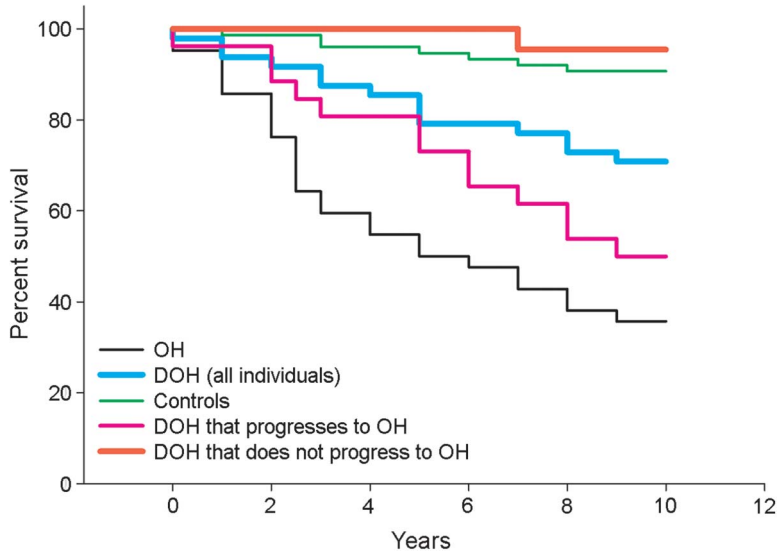
Report of mortality by initial and 10-year follow-up diagnosis of the individuals included in the study. The orange boxes represent the original diagnosis of those individuals tested in 2002–2003. Many individuals did not have a diagnosis at that time. During 10 years of follow-up, they were diagnosed with a number of different disorders. The yellow boxes represent the individuals alive after 10 years of follow up subdivided by orthostatic hypotension group (the delayed orthostatic hypotension group is subdivided into those who progressed to orthostatic hypotension and those who continued to have delayed orthostatic hypotension). The green boxes at the bottom describe the individuals who died over the 10 years of follow-up, by orthostatic hypotension group. OH = orthostatic hypotension. *Other diseases include depression, hypertension, thyroid dysfunction, dyslipidemia, and irritable bowel disease.

with DOH. The major findings are as follows: (1) over 10 years, 54% of individuals with DOH develop OH; (2) a substantial number develop neurodegenerative diseases, most commonly α-synucleinopathies; (3) the mortality in individuals with DOH is increased; and (4) the increase in mortality is associated with progression to OH, abnormalities in baseline autonomic test results, the presence of diabetes, and the development of an α-synucleinopathy. These data suggest that DOH is an earlier, milder form of OH that, with time, will progress to OH in more than half of the patients and carries a similar poor prognosis.

Streeten and Anderson,[1,4] who originally drew attention to DOH, suggested that the disorder may underlie a significant proportion of patients with chronic fatigue and the chronic fatigue syndrome. The present data indicate that in many patients the underlying disorders associated with DOH are more serious. At the time of original testing, disorders associated with DOH included diabetes (16%), cardiac disease (14%), and pure autonomic failure (2%). The remaining individuals were undiagnosed. After 10 years, the underlying etiologies associated with DOH during initial testing included diabetes (16%), cardiac disease (14%), synucleinopathies (26%), and a presumed medication adverse effect (28%). Sixteen percent were lost to follow-up.

Our data suggest that DOH falls along the continuum of severity and associated mortality risk associated with generalized autonomic dysfunction and with OH alone. The magnitude of the mortality in DOH approaches that associated with autonomic dysfunction in individuals with diabetes and other neurodegenerative disorders. Several studies have provided evidence of an increase in overall mortality and sudden death in patients with diabetic cardiovascular autonomic neuropathy.[6–8] Estimates for the mortality in diabetic autonomic neuropathy range from 27% to 56% over 5–10 years[8–11] and, in a pooled analysis of 15 studies, the

Figure 3 Kaplan-Meier survival curve



Mortality rates over time are reported for individuals with orthostatic hypotension (OH), individuals with delayed OH (DOH) (total, and identified by progression or no progression to OH), and controls.

relative risk for mortality was >3-fold in studies that defined diabetic cardiac autonomic neuropathy by the presence of 2 or more autonomic test abnormalities.[8] However, these studies of diabetic autonomic neuropathy did not address the mortality risk of OH alone. This was addressed specifically in a study of an Italian cohort with neurogenic OH evaluated at an autonomic laboratory in which the mortality was 42%.[12] The median follow-up of this cohort was 53 months and the majority of participants had α-synucleinopathies at the time of original testing.[12] While in unselected community-based studies OH has a lower but still significant morality risk,[13–16] a recent meta-analysis of these cohort studies reported a significant all-cause mortality-adjusted risk ratio of 1.4.[17] The mechanism underlying the increased mortality and the cause of death in most of these studies is not known and is likely to vary with the underlying population under study.

Table 2 Parasympathetic function and probability of delayed orthostatic hypotension progression

	No tests abnormal	One test abnormal	Two tests abnormal	Three tests abnormal	Total
Delayed OH, no progression	16	5	1	0	22
Delayed OH, progression to OH	2	2	5	17	26
Likelihood of progression to OH, %	11	28	83	100	—

Abbreviation: OH = orthostatic hypotension.
Three tests of parasympathetic function were performed on each patient during their baseline autonomic testing: Valsalva ratio, heart rate response to deep breathing, and heart rate response to standing (the 30:15 ratio). The probability of progressing from delayed orthostatic hypotension to orthostatic hypotension within 3 minutes is grouped by the number of abnormal tests. Normal or abnormal values were based on laboratory age- and sex-defined 95% confidence intervals for testing.

The present data reinforce the serious long-term implications of OH. Individuals in our cohort with OH at the time of original testing had a 10-year mortality rate of 64% and individuals with DOH that progressed to OH had a 10-year mortality rate of 50%. In contrast, those with DOH that did not progress to OH and our control group had 10-year mortality rates of <10%, values similar to the expected 10-year mortality rate (7%–9% for that age range) of the general population.[18] These findings suggest that, in our center, referral for autonomic testing alone does not predict an increase in mortality. Although overall mortality is associated with the development of specific underlying diseases, the progression to OH magnifies the risk, particularly in individuals with diabetes. In our study, diabetes with DOH carried a mortality risk over 4 times higher than having diabetes alone, while OH within 3 minutes with a diagnosis of diabetes carried a mortality risk over 5 times higher than having diabetes alone.

A subgroup of individuals with DOH had no disease progression and no associated increase in mortality. Over 70% of individuals in this DOH group had normal parasympathetic function; only 5% of this DOH group had more than 1 test of parasympathetic function in the abnormal range. These results are similar to those seen in the control group. Further, 68% of the individuals with DOH that did not progress to OH were treated with medications that could result in OH. This subgroup highlights the prognostic importance of normal parasympathetic autonomic test results in the setting of DOH and also suggests a possible intervention—discontinuation or modification of vasoactive medications. However, the long-term outcome of this group will require further study.

There are a number of limitations to our study. This was a retrospective review of data with some participants lost to follow up; 10-year follow-up autonomic testing data were available in >80% of individuals. Detailed information about the cause of death was not available in all participants and few had autopsies performed. Participants did not have autonomic testing repeated; therefore, we do not know if some people with DOH who did not progress to OH normalized over time. Also, the study is based on data derived from individuals referred for testing in a tertiary care center autonomic laboratory and may not be generalizable to a community-based cohort. In addition, our control group was not composed of healthy people but consisted of individuals referred for autonomic testing who were thus likely to have an increased risk of neurodegenerative disease, cardiac disease, and diabetes. The referral bias inherent to this control group could decrease the differences in

autonomic test results between controls and individuals with DOH.

DOH, like OH, is not a benign disorder. A substantial number of individuals progress to OH and develop α-synucleinopathies. The 10-year mortality rates for people with DOH approach those of individuals with OH. A subgroup with DOH does not have disease progression or increased risk of mortality. Many of these individuals have normal baseline parasympathetic autonomic tests results. Vasoactive medications may underlie the delayed OH in this subgroup.

AUTHOR CONTRIBUTIONS

Dr. Gibbons was involved in study design, data collection, data analysis, data interpretation, statistical analysis, and writing the manuscript. Dr. Freeman was involved in study design, data analysis, data interpretation, and manuscript revision.

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DISCLOSURE

C. Gibbons has received personal compensation for serving on scientific advisory boards of Pfizer and Grifols. R. Freeman has received personal compensation for serving on scientific advisory boards of Abbott, Astellas, Biogen, Dong, Johnson & Johnson, Lundbeck, PamLab, Pfizer, Spinifex, and Zallicus. Dr. Freeman receives funding from the NIH, National Institute of Neurological Disorders and Stroke, and NHLBI. Dr. Freeman has received research support from Impeto and Pamlab. Dr. Freeman has received personal compensation for his editorial activities (editor) with *Autonomic Neuroscience: Basic and Clinical*. Go to Neurology.org for full disclosures.

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