Independent Effects of Peripheral Nerve Dysfunction on Lower-Extremity Physical Function in Old Age

The Women's Health and Aging Study

HELAINE E. RESNICK, PHD, MPH
AARON I. VINIK, MBBCH, PHD, FCP, FACP
ANN V. SCHWARTZ, PHD
SUZANNE G. LEVEILLE, PHD
FREDERICK L. BRANCATI, MD, MHS
JENNIFER BALFOUR, PHD
JACK M. GURALNIK, MD, PHD

OBJECTIVE — To determine the role of peripheral nerve dysfunction (PND) in the disablement pathway.

RESEARCH DESIGN AND METHODS — Vibration perception threshold (VPT) was measured in 894 women aged ≥65 years, and those with normal peripheral nerve function and with mild, moderate, and severe PND were identified. Lower-extremity impairments included quadriceps strength (kilograms) and three progressively difficult balance tasks (able/unable). Functional limitations included rising from a chair (able/unable) and usual pace and fast-paced walking speeds (meters/second). Level of PND was related to impairments and functional limitations in linear and logistic regression models that controlled for potentially confounding factors, including reported diabetes.

RESULTS — Level of PND was associated with impaired balance (adjusted odds ratios: 2.21, 1.95, and 3.02 for mild, moderate, and severe PND, respectively, relative to normal, $P < 0.05$). PND was also associated with decrements in both usual and fast-paced walking speeds (−0.08, −0.08, and −0.15 m/s for usual pace and −0.13, −0.12, and −0.24 m/s for fast-paced walking speed for women with mild, moderate, and severe PND, respectively; $P < 0.01$ for all). Reported diabetes was not associated with these outcomes in the presence of PND. Some, but not all, of the association between PND and functional limitations was explained by the relationship between PND and impairments.

CONCLUSIONS — PND is significantly associated with both lower-extremity impairments and functional limitations in older women, and PND appears to have independent effects on functional limitations. The independent effect of diabetes on these outcomes may be limited when PND is considered. Further research is needed to determine if PND is causally related to disability in old age.

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From the MedStar Research Institute (H.E.R.), Washington, DC; the Epidemiology, Demography and Biometry Program (J.B., J.M.G.), National Institute on Aging, National Institutes of Health, Bethesda, Maryland; the Strelitz Diabetes Institutes (A.I.V.), Eastern Virginia Medical School, Norfolk, Virginia; the Department of Epidemiology and Biostatistics (A.V.S.), University of California at San Francisco, San Francisco, California; the Hebrew Rehabilitation Center for the Aged (S.G.L.), Boston, Massachusetts; and the Departments of Internal Medicine and Epidemiology (F.L.B.), the Johns Hopkins University, Baltimore, Maryland.

Address corrrespondence and reprint requests to Helaine E. Resnick, PhD, MPH, MedStar Research Institute, 108 Irving St., N.W., Washington, DC 20010. E-mail: her1@mhg.edu.

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H.E.R. is currently affiliated with the MedStar Research Institute, Washington, DC.

Abbreviations: OR, odds ratio; PND, peripheral nerve dysfunction; VPT, vibration perception threshold; WHAS, Women's Health and Aging Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Of physical limitations that occur with advancing age, lower-extremity limitations are particularly evident: 14.3% of Americans ≥65 years of age report difficulty walking—a proportion increasing to 34.9% for adults ≥85 years of age (1). Interest in loss of lower-extremity function with age relates to the observation that this loss predicts disability and loss of independence in the community (2,3). Accelerated decline in peripheral nerve function with age suggests that nerve function may influence functional decline, even in very old age (4).

Figure 1 is a modification of an existing framework of the pathway from disease to disability (5,6). Increasing with age and in the presence of diabetes, PND is characterized by loss of distal strength, impaired position sense, ataxia, and muscle atrophy, potentially contributing to lower-extremity functional limitations through impairments such as strength and balance (7–10).

Studies of PND show associations with gait abnormalities, ankle mobility, balance, and history of falls (11–14). However, these studies are limited by examination of clinic-based samples, no control of confounding, examination of only diabetic subjects, and underrepresentation of older adults (11–14). This article addresses these limitations and examines relationships between PND and both lower-extremity impairments and functional limitations. We hypothesized that older women with PND would be more impaired and have greater functional limitations in the lower extremity. We also examined if PND was associated with lower-extremity functional limitations through its effect on impairments or if PND had independent effects on functional limitations. The role of diabetes in this pathway was also examined.

RESEARCH DESIGN AND METHODS

Sampling and design

The Women's Health and Aging Study (WHAS) includes 1,002 moderately to severely disabled women ≥65 years of age.

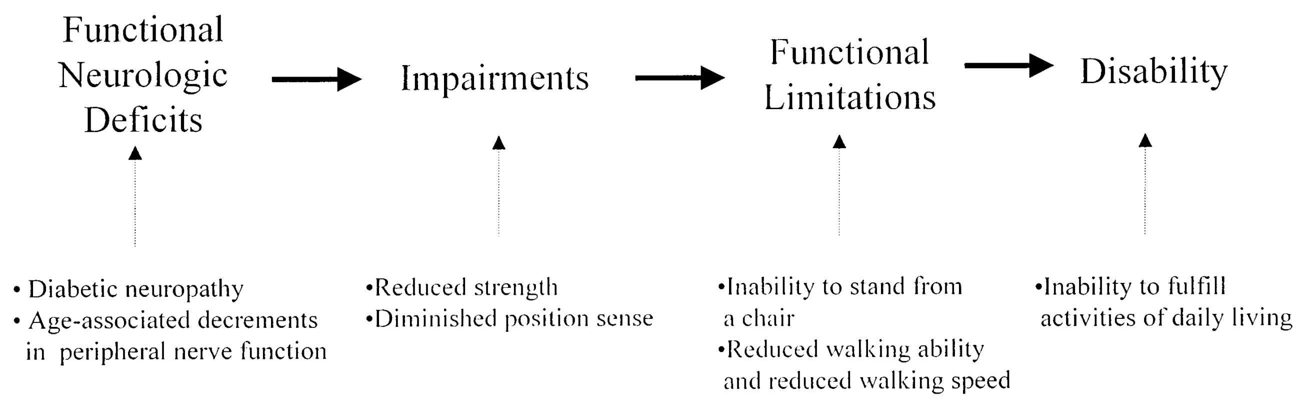

Figure 1—*Framework for the potential role of PND in development of disability in old age.*

Participants were selected from Medicare lists of 12 contiguous zip codes in Baltimore, Maryland, excluding those with severe cognitive impairment (15). Selection and characteristics of WHAS participants have been published (16,17). WHAS received approval from the Institutional Review Board of the Johns Hopkins University. Participants provided informed consent.

Large-fiber peripheral nerve function

Large-fiber sensory nerve function was quantified by vibration perception threshold (VPT) with the Vibratron II (Physitemp Instruments, Clifton, NJ). The Vibratron II measures sensitivity of the great toe in detecting vibratory stimuli. Higher values for VPT indicate that a stronger stimulus was needed to elicit a response, reflecting worse PND. The forced-choice protocol used in WHAS has been described and validated (16,18,19). Categories of PND are based on deviations from age-specific normal values: for adults >65 years of age, <3.43 U defines the upper limit of normal function, 3.43 to <4.87 U indicates mild dysfunction, 4.87 to <6.31 U indicates moderate dysfunction, and ≥6.31 U indicates severe dysfunction (18). Previous work in WHAS demonstrated the validity of these categories (4).

Lower-extremity impairments and functional limitations

Performance-based tests objectively assess physical abilities (20). Several lower-extremity performance tests potentially related to PND were collected in WHAS, including usual and fast-paced walking speeds and ability to stand from a chair. Potentially PND-associated impairments were also measured, including balance and quadriceps strength.

Usual and fast-paced walks. Participants stood at a starting line and then walked a 4-m course after a verbal command. Subjects could use walking aids, but not the assistance of another person. Usual pace and fastest possible pace were measured. Results were evaluated as meters/second.

Chair stand. Sitting in straight-back chairs with arms folded across their chests, participants were asked to stand from the chair. This task was evaluated as able/unable.

Balance. Static balance was evaluated with three progressively difficult stands: *1*) side-by-side: feet side by side, touching; *2*) semi-tandem: side of the heel of one foot touching the big toe of the other; *3*) tandem: heel of one foot in front of and touching the toes of the other. Maintaining the stand for 10 s constituted completion of the test. Balance tests were evaluated as able/unable.

Strength. Quadriceps strength was measured by dynamometer (Nicholas Manual Muscle Tester, model BK-7454, Burr Ridge, IL) (21,22). Participants pushed against the dynamometer as hard as they could, with the examiner pushing to break the contraction. Quadriceps strength was evaluated in kilograms.

Table 1—*Prevalence of impairments and functional limitations according to level of PND: WHAS*

	Level of peripheral nerve function			
Performance measure	Normal	Mild dysfunction	Moderate dysfunction	Severe dysfunction
Impairments				
Quadriceps strength*	13.5	12.9	12.8	12.9
Side/side stand†	9.6	18.0	23.9	20.9‡
Semi-tandem stand†	23.2	44.6	45.4	55.8‡
Tandem stand†	64.2	84.8	85.4	90.1‡
Functional limitations				
Chair stand†	8.8	17.9	18.9	30.6‡
Usual-paced walk§	0.65	0.57‖	0.58‖	0.51‖
Fast-paced walk§	1.01	0.89‖	0.90¶	0.78‖

Data are for women with a valid VPT measure. *Quadriceps strength expressed as age-adjusted kilogram. †Data are presented as unadjusted % of women who were unable to complete the task. ‡$P < 0.001$, trend. §Data are meters per second. ‖Means differ from normal function at $P < 0.001$. ¶Means differ from normal function at $P < 0.01$.

Sample selection

Of the 1,002 women in WHAS, 894 (89.2%) had valid VPT data. Of the 104 missing VPT data, 47 did not complete the protocol, 7 could not perform the test, 5 did not understand the instructions, 43 did not comply with the instructions, and 2 refused. More than 98 and 94% of the analysis sample had data for binary and continuous outcomes, respectively. Four additional women reported diabetes before age 30 years and were excluded.

Statistical methodology

For binary outcomes, the χ^2 trend test was used to study PND in relation to

Table 2—*Linear and logistic regression analyses relating level of PND* to prevalence of impairments and functional limitations: WHAS*

	Logistic regression models			
	Model 1†		Model 2‡	
Independent variable	β	OR (95% CI)	β	OR (95% CI)
Failure to complete single chair stand				
Mild PND	0.69	1.99 (1.19–3.33)	0.48	1.61 (0.84–3.07)
Moderate PND	0.72	2.06 (1.15–3.68)	0.018	1.19 (0.54–2.58)
Severe PND	1.35	3.84 (2.33–6.34)	1.29	3.62 (1.99–6.54)
Failure to complete side/side stand				
Mild PND	0.50	1.64 (0.99–2.73)	0.22	1.25 (0.65–2.41)
Moderate PND	0.79	2.20 (1.27–3.82)	0.51	1.67 (0.84–3.32)
Severe PND	0.58	1.78 (1.05–3.02)	0.46	1.58 (0.84–2.99)
Failure to complete semi-tandem stand				
Mild PND	0.75	2.12 (1.45–3.09)	0.50	1.65 (1.07–2.55)
Moderate PND	0.69	1.99 (1.28–3.11)	0.47	1.61 (0.97–2.66)
Severe PND	1.10	3.01 (2.01–4.51)	0.99	2.68 (1.71–4.20)
Failure to complete tandem stand				
Mild PND	0.88	2.42 (1.54–3.80)	0.80	2.21 (1.36–3.60)
Moderate PND	0.80	2.22 (1.27–3.88)	0.67	1.95 (1.07–3.55)
Severe PND	1.248	3.45 (1.95–6.09)	1.10	3.02 (1.65–5.51)

	Linear regression models					
	β	SEM (β)	*P*	β	SEM (β)	*P*
Quadriceps strength (kg)						
Mild PND	−0.68	0.44	0.12	−0.52	0.47	0.28
Moderate PND	−0.79	0.52	0.13	−0.06	0.57	0.92
Severe PND	−0.67	0.47	0.17	−0.32	0.51	0.54
Speed of usual-paced walk (m/s)						
Mild PND	−0.08	0.02	<0.001	−0.07	0.02	<0.01
Moderate PND	−0.08	0.02	<0.01	−0.04	0.02	0.15
Severe PND	−0.15	0.02	<0.001	−0.12	0.02	<0.001
Speed of fast-paced walk (m/s)						
Mild PND	−0.13	0.03	<0.001	−0.11	0.03	<0.01
Moderate PND	−0.12	0.04	<0.01	−0.05	0.04	0.19
Severe PND	−0.24	0.04	<0.001	−0.20	0.03	<0.001

*Relative to women with normal peripheral nerve function. †Model 1 is adjusted for age. ‡Model 2 is adjusted for age, reported diabetes, BMI, visual acuity, arthritis, and history of stroke. Adjustment for multiple confounders reduced the number of participants available for analysis as follows: chair stand, *n* = 755; side/side stand, *n* = 761; semi-tandem stand, *n* = 761; tandem stand, *n* = 760; quadriceps strength, *n* = 705; usual-paced walk, *n* = 754; fast-paced walk, *n* = 731.

lower-extremity impairments and functional limitations. For continuous outcomes, generalized linear models were used to examine PND in relation to age-adjusted mean performance levels. Logistic and linear regression models were used to examine PND in relation to impairments and functional limitations, adjusted for age and potential confounders. The normal PND group was considered the reference. To determine if PND influenced functional limitations by influencing impairments, models predicting functional limitations included both impairments and PND. Reported diabetes was examined to determine its effect in the presence of PND. Potential confounders included BMI, osteoarthritis of the hips or knees (present/absent), history of stroke, and visual acuity.

RESULTS — More than one-quarter of the sample was ≥85 years of age and 18.5% reported diabetes. Mean BMI was 28.4 kg/m^2, 56% had arthritis, 12.3% reported history of stroke, and 68% had visual acuity 20/40 or better. Furthermore, 42% had normal peripheral nerve function and 23.9, 14.5, and 19.5% had mild, moderate, and severe dysfunction, respectively. A PND-associated trend of increasing impairment was observed for all balance tests (Table 1). For example, 23.2% of women with normal nerve function failed to complete the semi-tandem stand, whereas 55.8% of women with severe PND failed to complete it. Within level of PND, more women failed to complete balance tests as test difficulty increased: 20.9% of women with severe PND could not complete the side-by-side stand, but 90.1% of women with severe PND could not complete the tandem stand. Quadriceps strength was not associated with PND.

A PND-associated trend was observed also for the chair stand. Failure to complete this test increased from 8.8% in the normal PND group to 30.6% in the severe group. Women at each PND level had significantly slower walking speeds than those in the normal group. Usual walking speed was 0.51 and 0.65 m/s in the severe PND and normal groups, respectively. Fast-paced walking speed yielded similar results. Women with mild and moderate PND had similar walking speeds, but these speeds were significantly slower than those of the normal group.

Regression model 1 is adjusted for age, and model 2 is adjusted further for reported diabetes and potential confounders (Table 2). Model 1 indicated that PND was associated with prevalence of impairments and functional limitations, and the magnitude of odds ratios (ORs) generally increased with increasing PND. Adjustment for confounders attenuated the ORs somewhat (model 2), but severe PND remained associated with a threefold increased odds of inability to complete the chair stand and tandem stand. PND also remained associated with inability to complete the semi-tandem stand. For these outcomes, the ORs for mild and moderate PND were similar, but the OR for severe PND was considerably larger. Reported diabetes was not associated with these outcomes in the presence of PND.

Age-adjusted decrements in walking speed associated with mild and moderate PND were similar (−0.08 m/s for usual

Table 3—*Regression analysis relating level of PND* and impairments to prevalence of functional limitations: WHAS*

Independent variable	β	OR	95% CI
Logistic regression model			
Failure to complete single chair stand			
Mild PND	0.49	1.64	0.92–2.94
Moderate PND	0.65	1.91	1.01–3.63
Severe PND	1.13	3.09	1.74–5.46
Quadriceps strength	−0.11	0.90	0.43–1.27
Unable to complete tandem stand	2.20	8.99	2.73–29.67
	β	SEM (β)	*P*
Linear regression models			
Usual-paced walk (m/s)			
Mild PND	−0.05	0.02	<0.05
Moderate PND	−0.05	0.02	<0.05
Severe PND	−0.11	0.02	<0.001
Quadriceps strength	0.02	0.00	<0.001
Unable to complete tandem stand	−0.16	0.02	<0.001
Fast-paced walk (m/s)			
Mild PND	−0.09	0.03	<0.01
Moderate PND	−0.07	0.04	0.05
Severe PND	−0.17	0.04	<0.001
Quadriceps strength	0.03	0.003	<0.001
Unable to complete tandem stand	−0.22	0.03	<0.001

Data are age-adjusted. *Relative to women with normal PND.

pace and −0.13 and −0.12 m/s for fast pace, respectively), but decrements for severe PND were larger (−0.15 and −0.24 m/s for usual and fast pace, respectively). Reported diabetes was not associated with walking speed in the presence of PND.

If PND were associated with functional limitations only through impairments, the apparent effect of PND would be diminished or eliminated when examined together with impairments in models predicting functional limitations. However, PND remained significantly associated with functional limitations in the presence of impairments, and this association persisted after further adjustment for confounders (Table 3). Reported diabetes was not significant in these models (data not shown). Table 4 demonstrates that although a portion of the association between PND and lower-extremity functional limitations appeared to operate through impairments, impairments did not explain all or even a majority of these associations.

CONCLUSIONS — We demonstrate associations between large-fiber PND and impaired balance and functional limitation in walking speed and ability to rise from a chair. An association between PND and balance has been shown in studies of diabetic individuals (23–25), and relationships between diabetic neuropathy and gait abnormalities have been published (11,12). We extend findings from diabetic populations to a population of older adults whose PND occurs both in the presence and absence of diabetes. Indeed, >80% of our sample did not report diabetes, yet associations for PND were evident when adjusted for diabetes.

These results provide a new framework in which PND contributes to functional limitation through PND-associated impairments. Impairment in PND-associated abilities, such as balance and strength, may lead to functional limitations and, ultimately, to disability. We showed that PND-associated impairments did not explain all of the association between PND and functional limitations, suggesting that PND may have independent effects on functional limitations. An alternative explanation is that PND influences functional limitations through pathways other than those examined here.

Diabetes is associated with decreased function in older adults (26–28). One study suggested that pain and light-touch sensation account for associations between diabetes and functional limitations (28). Our work on PND and diabetes in WHAS showed significant associations between reported diabetes and PND (4), but our finding of no association between diabetes and functional limitations when accounting for PND suggests a limited direct role of diabetes with respect to the outcomes. It should be emphasized that diabetes was ascertained by self-report in WHAS, not by fasting glucose. Misclassification would have underestimated the number of diabetic women, potentially limiting the power to detect an association between diabetes and function.

WHAS included three progressively difficult balance tasks, which allowed examination of PND on a single test, as well as the effect of increasing test difficulty within PND level. PND was associated with greater impairment on all balance tests. That 90% of women with severe PND could not complete the tandem stand suggests that this simple test may be specific for identifying individuals with the most severe deficits. Our findings are consistent with previous studies demonstrating associations between PND measured by VPT and impaired proprioception (24,25,29). A key question that cannot be answered here is whether further adjustment for PND-associated impairments would have abolished the residual association between PND and functional limitations.

Conduction velocity of the median nerve has been associated with decrements in grip strength, indicating a link between peripheral nerve function and strength (30). We did not observe an association between PND measured by VPT and quadriceps strength. This negative finding was not surprising, because VPT is a measure of sensory function, not motor nerve function, and an association between VPT and quadriceps strength would have been unexpected. However, it should be noted that PND follows a distal-to-proximal pattern, making a potential PND-associated change in quadriceps strength a relatively late manifestation of PND—another potential explanation for our negative findings. Quadriceps strength might have been associated with motor nerve function had such a measure been collected in WHAS. Supporting this possibility are findings from previous studies showing age-associated decrements in motor nerve function and loss of muscle strength (31,32). To fully explore the role of PND in the disablement pathway, availability of data on both sensory and motor function as well as specific impairments related to these distinct modalities is ideal.

Table 4—*Comparison of age-adjusted and age- and impairment-adjusted models relating PND to lower-extremity physical function: WHAS*

Functional limitation	% Change in β	% Change on OR attributable to specific impairments	Decrement in gait speed attributable to specific impairments (m/s)
Logistic regression models			
Chair stand			
Mild PND	−28	−18	—
Moderate PND	−10	−7	—
Severe PND	−16	−20	—
Linear regression			
Usual-paced walk			
Mild PND	−39	—	−0.032
Moderate PND	−37	—	−0.029
Severe PND	−30	—	−0.045
Fast-paced walk			
Mild PND	−60	—	−0.075
Moderate PND	−36	—	−0.042
Severe PND	−30	—	−0.072

Walking is critical for maintenance of independence in the community (2). Simple activities such as housework involve walking, making the PND–walking association important for older adults' independence. Unlike housework, where walking speed is not crucial, there are instances in community living when achieving a minimum gait speed is critical for safety. An example is crossing the street at signaled intersections. In a study of adults ≥72 years of age, <1% of participants had walking speeds sufficient to cross a typical signaled intersection (33). The association between PND and walking speed suggests that interventions aimed at reducing the functional consequences of PND may enhance older adults' maintenance of independence.

The WHAS cohort consists exclusively of women, precluding examination of sex effects. Despite this limitation, it is known that women live longer than men (1) and that older women experience more disability than older men (34), making potentially modifiable disability risk factors in older women a public health priority. WHAS participants were selected based on disability, making them somewhat unrepresentative of women who are ≥65 years of age. However, WHAS provides a unique opportunity to study PND and physical abilities in a large sample of individuals whose disabilities could have masked these associations had they been weak.

In summary, this study demonstrates significant cross-sectional associations between large-fiber peripheral nerve dysfunction and both lower-extremity impairments and functional limitations. PND-associated impairments in balance appear to account for some, but not all, of the association between PND and functional limitations. Further research is needed to distinguish the roles of sensory and motor nerve function on physical limitations and disability and whether either or both of these modalities are causally related to disability in old age.

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