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Diabetic Family History is Associated with Severity of Peripheral Neuropathy

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Abstract

Background

Clinicians lack tools to determine a patient's risk for diabetic peripheral neuropathy (DPN). This study examined the relationship between severity of DPN and family history of diabetes and DPN.

Methods

The Michigan Neuropathy Screening Instrument (MNSI) was used to collect symptom and physical exam data from consenting diabetic and control (n=293) patients. Family history of diabetes, DPN and major complications were collected going back two generations. Relevant additional characteristics were mined from patient medical records.

Results

Between patients who did and did not meet MNSI criteria for neuropathy, there were significant differences in comorbidities, including cardiac (P<.0001), renal (P=.006), PVD (P<.0001), and thyroid (P=.027). Patients with history of diabetes on both sides (P=.032) or siblings (P<.0001); history of neuropathy on their maternal (P=.026), paternal (P=.002), both sides (P=.002) or siblings (P=.002); history of amputations on their maternal (P=.039) or paternal side (P=.162); or a history of ulcers on their maternal side (P=.030), paternal side (P=.005) or both sides (P=.046) were more likely to meet MNSI criteria for neuropathy. MNSI criteria for neuropathy was independently associated with history of cardiac or PVD comorbidities, and an MNSI score in the upper quartile was associated with diabetic siblings (OR=10.96).

Conclusion: Family history of diabetes, DPN, and major complications was associated with neuropathy and also stronger degree of neuropathy. Family history, specifically diabetic siblings, cardiac and PVD comorbidities are independent risk factors for developing DPN. Clinicians should gather detailed family history and relevant comorbidities to optimize prevention of severe DPN in diabetics.

Keywords:Type 2; Diabetic peripheral neuropathy; Family history of diabetes; MNSI; Complications

Introduction

Over 29 million Americans are diabetic with an additional 86 million who are pre-diabetic. The incidence in diabetes dramatically increased from 1990 to 2007 to 7.8 per 1000 adults, with a recent reduction to 6.0 per 1000 adults in 2017. Diabetic peripheral neuropathy (DPN) continues to be the leading cause of complications of diabetes mellitus, as 50% of diabetic patients worldwide will develop DPN [1–8]. DPN is the leading cause of disability due to foot ulceration and amputation, gait disturbance, and fall-related injuries, and approximately 20-30% of these patients suffer from neuropathic pain [2–4, 6, 9, 10]. Furthermore, DPN significantly lowers quality of life and substantially increases healthcare costs [9]. Those with DPN experience a two-fold increase in health-care costs related to diabetes annually, and those with severe painful neuropathy experience a fourfold increase [11]. 27% of healthcare costs of diabetes can be attributed to DPN, or roughly $66 billion [12]. It is clear that DPN is a significant problem for both patients and providers alike.

It has previously been shown that early subclinical detection of DPN, by assessing genetic predisposition as well as metabolic control and physiology of diabetic patients, is critical in facilitating early intervention and prevention of the potentially serious consequences [2, 13, 14]. Recent studies have shown promise in the use of genome-wide association studies and next-generation sequencing techniques to identify and facilitate treatment for individuals with type 2 diabetes, but this technology seems to be several years away from widespread use [13,15,16]. A study evaluating how a patient's family history, in particular with regards to DPN, affects a patient's likely progression and severity of DPN could aid clinicians in determining more targeted and personalized treatment options in a manner more compatible with current clinic capabilities. We sought to determine whether or not this focused family history would be a tool that is able to effectively and feasibly identify individuals with a high risk of developing DPN.

Methods

Data Collection

Major eligibility criteria for patients included fluency in English, age 18 to 70, and those with established care at the University of Illinois Hospital and Health Sciences System (UIH). After receiving approval by the local institutional review board, patients who were at UIH for a scheduled clinic visit at either the Orthopedic or Podiatry clinics were recruited. Written informed consent was obtained from all patients. Trained staff evaluated patients for neuropathy using the Michigan Neuropathy Screening Instrument (MNSI). The MNSI includes a questionnaire that collects information about subjective symptoms of neuropathy experienced by the patient including tingling, burning, and numbness in the lower extremity. The MNSI also includes a physical exam section consisting of visual inspection of the feet, assessing the presence of bilateral Achilles reflexes, testing of vibration perception using a tuning fork at the hallux, and sensory sensitivity using monofilament on each foot. Patient responses were then converted and recorded as an MNSI score.

Family history information was collected by having the patient complete a written family-tree either with the patient during their clinic visit or over the phone shortly after the appointment. The family tree detailed history of diabetes, DPN, ulceration, and/or amputation dating back two generations. This included grandparents, aunts, uncles, parents, and siblings. The family history was divided into anyone on the mother's side (maternal), anyone on the father's side (paternal), both maternal and paternal, and siblings. Electronic medical records were also subsequently reviewed for basic demographic information, relevant comorbidities, medications, and lab values.

Statistical Analysis

Patient information was de-identified and codified on encrypted software. The sample was analyzed based on two groupings using SAS software. The first was based on if they met the MNSI criteria for neuropathy by having a score greater than 2.5. Univariate regression analyses compared the two groups based on patient characteristics and comorbidities. Patient factors included age, ethnicity, sex, location of neuropathy, recent hba1c levels based on quartiles, smoking status (never smoked, former, current), BMI in quartiles, amount of exercise (none, less than or greater than 150 minutes a week), and usage of neuropathic medicine. Relevant comorbidities with cardiac, pulmonary, renal, thyroid, and peripheral vascular disease (PVD) issues were used in the analysis. Univariate analyses compared the two groups based on family history of diabetes, DPN, ulceration, and/or amputation. The same univariate regression analyses were performed for the sample by grouping of severity of neuropathy. Patients were divided into quartiles based on MNSI score. The top quartile representing the upper 25th percentile w compared to the rest of the patients in the bottom 75th percentile. To look for independent associations, multivariate regression analyses for both groupings were performed comparing them based on the same patient factors, comorbidities, and family history as described above. Data are reported as absolute numbers or percentages. Statistical significance was accepted at a P-value < 0.05.

Results

Patient characteristics and relevant comorbidities are summarized in Table 1. From the sample, 197 (67.5%) of participants met the MNSI criteria for neuropathy ("neuropathic"), while 95 participants (32.6%) did not ("non-neuropathic"). One patient in the non-neuropathic group had neuropathy in their lower extremities but failed to meet MNSI criteria. 61.4% of the neuropathic group had type 2 diabetes, compared to 17.9% of the non-neuropathic group ($p < .0001$). In the neuropathic group, neuropathy was found more commonly in the lower extremities (15.2%) than in the upper extremities (2.0%) or both (11.2%).

The neuropathic and non-neuropathic group had similar characteristics by sex and race. There were comparable proportions of male (39.6% vs. 35.8%) and female (60.4% vs. 64.2%) participants between the neuropathic and non-neuropathic group. Patients with and without neuropathy identified as black (62.9% vs. 56.8%), white (17.8% vs. 17.9%), Hispanic/Latino (10.2 vs. 8.4%), Asian (1.0% vs. 6.3%) and other (8.1% vs. 10.5%). Patient age ranged from 18 to 70 years. The non-neuropathic group was younger with the majority between 18-42 (56.8% vs. 9.15%). The neuropathic group had no majority quartile, with 58 (29.4%) between 42-54 years, 67 (34.0%) between 54-61 years, and 54 (27.4%) between 61-70 years old.

Smoking was more prevalent in the neuropathic group, with more current smokers (26.8% vs. 18.5%) and former smokers (20% vs. 8.6%). Most recent HbA1c levels in patients who did and did not meet MNSI neuropathy criteria were categorized as non-diabetic (16.5% vs. 43.3%), prediabetes (22.8% vs. 20%), controlled diabetes (49.6% vs. 30%), and uncontrolled diabetes (11% vs. 6.7%). Patients in the neuropathic group had a significantly increased use of neuropathic medicine (49.7% vs. 31.6%, $P < 0.01$). Patients that did and did not meet MNSI criteria had differing prevalence of comorbidities: cardiac (62.2% vs. 32.6%), renal (20% vs. 7.4%), peripheral vascular disease (30.3% vs. 9.5%), and thyroid (10.8% vs. 3.2%). On the other hand, meeting the MNSI criteria for neuropathy was not associated with differing exercise levels, steroid use, or the presence of pulmonary comorbidities.

The presence of family history of diabetes, diabetic peripheral neuropathy, and its complications (amputation, ulcers) grouped by neuropathic and non-neuropathic patients are summarized in Table 2. For family history of diabetes, patients that did and did not meet MNSI neuropathy criteria had similar prevalence of isolated maternal history (58.2% vs. 48.4%) and isolated paternal history (51.6% vs. 44.2%). There were significantly more neuropathic patients who had either maternal and paternal family history (31.2% vs. 19.1%, $P < 0.05$) or a sibling history (46.9% vs. 21.1%, $P < 0.0001$) of diabetes.

Table 1: Univariate analysis of patient characteristics for adults tested for neuropathy using the MNSI.

	Non-neuropathic (n = 95)		Neuropathic (n = 197)		
	n	%	n	%	P
Patient Characteristics and Comorbidities					
Diabetes	17	17.9	121	61.4	<.0001
Location of Neuropathy					
None	94	98.9	141	71.6	<.0001
Lower Extremity	1	1	30	15.2	
Upper Extremity	0	0	4	2	
Lower and Upper	0	0	22	11.2	
Extremity					
Sex					
Male	34	35.8	78	39.6	0.531
Female	61	64.2	119	60.4	
Race					
Black	54	56.8	124	62.9	0.108
White	17	17.9	35	17.8	
Hispanic/Latino	8	8.4	20	10.2	
Asian	6	6.3	2	1	
Other	10	10.5	16	8.1	
Age					
18-42	54	56.8	18	9.1	<.0001
42-54	12	12.6	58	29.4	
54-61	12	12.6	67	34	
61-70	17	17.9	54	27.4	
Smoking Status					
Never smoked	59	72.8	85	53.1	0.009
Current smoker	15	18.5	43	26.8	
Former smoker	7	8.6	32	20	
HbA1c					
Non-diabetic	13	43.3	21	16.5	0.014
Prediabetes	6	20	29	22.8	
Controlled	9	30	63	49.6	
Uncontrolled	2	6.7	14	11	
Exercise					
No exercise	14	37.8	53	46.9	0.409
<150 minutes/week	5	13.5	19	16.8	
>150 minutes/week	18	48.6	41	36.3	
Obese	48	50.5	139	70.6	0.0008
Cardiac Comorbidity	31	32.6	122	62.2	<.0001
Pulmonary Comorbidity	16	16.8	46	23.5	0.195
Renal Comorbidity	7	7.4	39	20	0.006

Peripheral Vascular Disease Comorbidity	9	9.5	59	30.3	<.0001
Thyroid Comorbidity	3	3.2	21	10.8	0.027
Steroid Use	23	24.2	34	18	0.217
Neuropathic Medicine Use	30	31.6	94	49.7	0.004

Table 2: Patient family history for diabetes and complications for adults tested for neuropathy using the MNSI.

	Non-neuropathic (n = 95)			Neuropathic (n = 197)		
	n	%		n	%	P
Family History of Diabetes						
Maternal History	46		48.4	114	58.2	0.117
Paternal History	42		44.2	98	51.6	0.274
Maternal and Paternal History	18		19.1	59	31.2	0.032
Sibling History	20		21.1	92	46.9	<.0001
Family History of DPN						
Maternal History	17		17.9	59	30.1	0.026
Paternal History	11		11.6	54	28.3	0.002
Maternal and Paternal History	1		1.1	22	11.6	0.002
Sibling History	4		4.26	33	17.9	0.002
Family History of Amputation						
Maternal History	4		4.2	23	11.7	0.039
Paternal History	4		4.2	30	15.2	0.006
Maternal and Paternal History	0		0	4	2	0.162
Sibling History	1		1.1	10	5.1	0.091
Family History of Ulcers						
Maternal History	6		6.3	30	15.2	0.03
Paternal History	4		4.2	31	15.7	0.005
Maternal and Paternal History	0		0	8	4.1	0.046
Sibling History	2		2.1	12	6.1	0.135
DPN = Diabetic Peripheral Neuropathy						

Neuropathic patients had significantly greater proportion of all types of family history related to diabetic peripheral neuropathy -- isolated maternal (30.1 vs 17.9, $P < 0.05$), isolated paternal (28.3% vs. 11.6%, $P < 0.01$), both maternal and paternal (11.6% vs. 1.1%, $P < 0.01$), and sibling history ($P < 0.01$). Similarly, patients who met MNSI criteria for neuropathy had significantly greater proportion of family history of amputation: isolated maternal (11.7% vs. 4.2%, $P < 0.05$) and isolated paternal (15.2% vs. 4.2%, $P < 0.01$). There were similar proportion of sibling history and both parental history of amputations between neuropathic and non-neuropathic patients. Isolated maternal, isolated paternal and both maternal and paternal history of ulcers were significantly associated with neuropathic patients compared to non-neuropathic patients ($P < 0.03$, $P < 0.01$, $P < 0.05$, respectively). Patients who did and did not meet MNSI criteria for neuropathy had similar proportion of sibling history of ulcers (6.1% vs. 2.1%).

The same patient characteristics and relevant comorbidities were analyzed between adults with MNSI scores in the bottom 75th percentile and in the top 25th percentile of the sample, summarized in Table 3.

The two groups had significantly different characteristics by race and age ($P < 0.05$). Patients in the top 25th and bottom 75th percentile identified as black (53.1% vs. 66.2%), white (12.2% vs. 19.6%), Hispanic or Latino (20.4% vs. 6.8%), Asian (2% vs. 0.7%) and other (12.2% vs. 6.8%). However, the two groups had similar proportions based on sex, location of neuropathic, presence of diabetes, smoking status, amount of exercise, and obese BMI (results not shown). Based on pertinent comorbidities, those in the top 25th and bottom 75th percentile of MNSI scores were comparable related to cardiac, pulmonary, peripheral vascular

Table 3: Patient characteristics for adults with MNSI score in bottom 75th and top 25th percentile

	MNSI Score Lower 75th		MNSI Score Top 25th		P
	n	%	n	%	
Race					
Black	98	66.2	26	53.1	0.0274
White	29	19.6	6	12.2	
Hispanic/Latino	10	6.8	10	20.4	
Asian	1	0.7	1	2	
Other	10	6.8	6	12.2	
Age					
18-42	16	10.8	2	4.1	0.048
42-54	38	25.7	20	40.8	
54-61	56	37.8	11	22.4	
61-70	38	25.7	16	32.7	
HbA1c					
Non-diabetic	16	17.6	5	13.9	0.0011
Prediabetes	28	30.7	1	2.8	
Controlled	41	45.1	22	61.1	
Uncontrolled	6	6.6	8	22.2	
Renal Comorbidity	24	16.4	15	30.6	0.038
MNSI = Michigan Neuropathy Screening Instrument					

Table 4: Patient family history for adults with MNSI score in bottom 75th and top 25th percentile

	MNSI Score Lower 75th		MNSI Score Top 25th		
	n	%	n	%	P
Family History of Diabetes					
Maternal History	78	52.7	36	75	0.005
Maternal and Paternal History	39	27.3	20	43.5	0.039
Family History of DPN					
Maternal History	37	25.2	22	44.9	0.009
Family History of Amputation					
Maternal History	11	7.4	12	24.5	0.003
Family History of Ulcers					
Maternal History	17	11.5	13	26.5	0.011
Sibling History	6	4.1	6	12.2	0.038

disease and thyroid conditions. There was only a significant difference in the presence of renal comorbidity, with 24 patients (16.4%) in the bottom 75th percentile and 15 patients (30.6%) in the top 25th percentile ($P < 0.05$).

The presence of family history of diabetes, diabetic peripheral neuropathy and its complications (amputation, ulcers) grouped by patients of the top 25th and bottom 75th percentile of MNSI scores are summarized in Table 4.

Maternal history of diabetes (75% vs. 52.7%, $P < 0.01$), peripheral neuropathy (44.9% vs. 25.2%, $P < 0.01$), amputations (24.5% vs. 7.4%, $P < 0.01$) and ulcers (26.5% vs. 11.5%, $P < 0.01$) were significantly higher in the group corresponding to the top 25th percentile of MNSI scores compared to those in the bottom 75th percentile. Having both paternal and maternal history of diabetes

were significantly associated with patients in the top 25th percentile ($P < 0.05$). Of note, sibling history was significantly associated only with the complication of ulcers, with 6 patients (12.2%) in the top 25th and 6 patients (4.1%) in the bottom 75th percentile. Otherwise, siblings and paternal history of diabetes or any complications were comparable between the two groups (results not shown).

Multivariate logistic regression analyses were performed for each of the patient characteristics, comorbidities and family history of diabetes or any of its complications, comparing patients with and without neuropathy (Table 5). The diagnosis of neuropathy via MNSI was independently associated with history of cardiac ($P < 0.01$) or PVD ($P < 0.05$) comorbidities. Similarly, multivariate logistic regressions were performed for those in the top 25th and bottom 75th percentile of MNSI scores for each of the patient factors, comorbidities and family histories [Table 5]. Having an MNSI score in the top 25th percentile was only independently associated with having a sibling history of diabetes ($P < 0.01$).

Table 5: History of cardiac issues or PVD as a risk factor for a diagnosis of neuropathy, while MNSI score in the top 25th percentile was independently associated with a sibling with diabetes.

	Adjusted OR (95% CI)	P Value
Diagnosis of peripheral neuropathy		
Cardiac Comorbidities	33.14 (3.21 – 342.49)	0.003
PVD Comorbidity	16.57 (1.11 – 248.22)	0.042
MNSI in Upper 25th Percentile		
Sibling with Diabetic History	10.96 (2.14 – 56.25)	0.004

Discussion

Our study found a number of comorbidities that were associated with the group of patients with neuropathy, including those related to cardiac, renal, PVD and thyroid conditions. Of these, cardiac and PVD comorbidities were independently associated as a risk factor for developing neuropathy. The cardiac comorbidity risk confirms the study findings of Ybarra-Munoz et. al, which found that diabetics with cardiovascular disease had an increased risk of developing DPN with a ten-year follow-up [17]. The PVD comorbidity risk falls in line with the findings in The Diabetes Control and Complications Trial [18]. The trial discovered that patients with PVD and diabetes were five to ten times more likely to have a major amputation compared to patients with only PVD. Taken together, our findings suggest that a patient with diabetes and PVD is at increased risk for developing neuropathy compared to diabetics without PVD, which could then later progress to a major amputation. Similarly, identifying a patient with both cardiovascular disease and diabetics as having increased risk for DPN could aid clinicians with focused control and treatment so to prevent such complications.

The strong genetic basis for type 2 diabetes is well-established, with an increased risk of developing diabetes if there is first-degree family history [19, 20]. This risk is seen especially if there is a maternal history and increases further if both parents have diabetes [21]. Our study extended these conclusions to look at how family history of not only diabetes but also its complications could be associated with a patient's risk of developing complications of diabetes. Our study showed that neuropathic patients were more likely to have significant family history of diabetes and complications such as DPN, amputations, and ulcers. In particular, maternal family history was associated with neuropathic patients in every category studied. This contrasts Scheffel et. al, who found no association between maternal diabetic history and prevalence of microvascular or macrovascular chronic complications [22]. Our study had a more robust screening instrument using the MNSI, which takes into account both subjective patient symptoms as well as physical testing of strength, presence of Achilles reflexes, vibration, and sensory sensitivity.

We had initially hypothesized that having greater strength of family history in diabetes and complications would be associated with greater severity of neuropathy. Molyneaux et. al found that a greater number of affected family members with diabetes was strongly associated with an earlier onset of developing diabetes [23]. This suggests a cumulative risk of developing diabetes based on family history. However, they did not find an association between strength of family history and prevalence of neuropathy. Our study had similar findings, as greater family histories such as both paternal and maternal were not associated with neuropathy. The lack of connection extended to the diabetic complications of amputation and ulcer as well. Instead, we found that only a sibling history of diabetes was independently associated with having a greater degree of neuropathy, indicated by a MNSI score for neuropathy in the top 25th percentile. This has pertinent implications for clinicians in evaluating risk of diabetic complications in patients. While strength of family history of diabetes is relevant in determining patient risk of diabetes, the history of first-degree relatives, especially siblings, should be taken into when determining risk of diabetic complications could allow clinicians to more accurately identify patients that should have tighter glycemic control and screening.

Conclusions

In conclusion, among diabetic patients, we found that the presence of family history of diabetes, diabetic peripheral neuropathy, and its complications was associated with not only neuropathy but also a stronger degree of DPN. While no type of family history was independently associated with DPN, family history specifically sibling history of diabetes was independently associated with a stronger degree of neuropathy. In addition, cardiac and PVD comorbidities were independently associated as a risk factor for developing neuropathy. It is critical for clinicians to recognize the utility in gathering thorough patient and family history from diabetics and how such histories help clinicians better characterize patient risk of developing DPN. Our findings suggest that clinicians could appropriately offer appropriate counseling for those patients who are at increased risk. Clinicians could therefore help prevent diabetic patients from developing DPN and suffering a multitude of complications if they are able to offer suitable preventive advice and services.

Author Contributions

UN and AH recruited study participants, collected symptom, physical exam and family history, codified patient information and wrote the manuscript. AH analyzed and interpreted the patient data. AP wrote the institutional review board proposal and recruited researchers. GM, AM, MS and MG allowed patient recruitment during their clinics. MS and MG were major contributors in editing the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

The authors declare that they have no competing interests.

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