Original Article

A clinical study of the association and risk factors for lower limb neuropathy in patients with diabetic retinopathy

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Abstract

Purpose: Association of peripheral neuropathy with diabetic retinopathy is known but the relationship of preclinical neuropathy with various grades of retinopathy is not well documented. This study evaluated the association of preclinical peripheral neuropathy using nerve conduction studies with various grades of retinopathy. **Methods:** Cases of diabetic retinopathy of various grades but asymptomatic for peripheral neuropathy underwent nerve conduction studies of the lower limbs using Caldwell machine and Sierra wave software. The risk factors for retinopathy and association of neuropathy with various grades of retinopathy were analyzed by bivariate and multivariate regression analysis. **Results:** The overall prevalence of neuropathy was 75.6% (sensory 58.54% and combined motor and sensory 17.1%) with increase in prevalence with increase in severity of retinopathy. Duration was positively associated with neuropathy (OR = 1.13, 95% CI = 1.02–1.24; P = 0.012); moderate nonproliferative diabetic retinopathy (NPDR) (OR = 5.60, P = 0.002), severe and very severe NPDR (OR = 5.8, P = 0.041), and PDR (OR = 16.05, P = 0.000) were significantly at higher risk for having neuropathy as compared to mild NPDR. **Conclusion:** Duration and severity of retinopathy are important risk factors for peripheral neuropathy. There is a high prevalence of peripheral neuropathy among diabetics with retinopathy especially with severe grades, when neuropathy is diagnosed using nerve conduction studies.

Keywords: Diabetes, nerve conduction, peripheral neuropathy, retinopathy

Introduction

With the rise in the incidence of diabetes worldwide, diabetic retinopathy has become one of the major causes of blindness.[1] The management of diabetic retinopathy is a complex and multipronged strategy which includes systemic glycemic control, laser treatment, intravitreal injections, and surgery.[2] The management can be delayed and sometimes confounded by coexisting systemic complications such as nephropathy and peripheral neuropathy.[3] The ocular fundus is unique as it facilitates visualization and grading of diabetic microangiopathy affecting the retinal vasculature. Since patients of type 2 diabetes are asymptomatic for prolonged periods with an undetected disease, fundus evaluation very often leads to the initial diagnosis of diabetes.[4] Similarly, the eye can be a pointer toward other microangiopathic complications and this association of retinopathy with nephropathy and neuropathy has been documented in several studies.[5-7] This is especially important in case of peripheral neuropathy which may be asymptomatic initially and difficult to detect clinically.[8,9] Studies on the prevalence of peripheral neuropathy among diabetics have reported widely differing figures.[10-12] The prevalence of peripheral neuropathy is estimated to be between 6%

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and 51% among adults.[13] The difference is partly due to the different demographic population studied and also due to the different methods used to detect the neuropathy.[14] While clinicophysiological tests for peripheral neuropathy are easier to administer, nerve conduction studies are more objective and reproducible in standard labs.[15] It may also detect subclinical neuropathy at the asymptomatic stage. However, these tests are more expensive and not widely available. Considering the reported association between retinopathy and neuropathy, nerve conduction studies among diabetics who have already developed retinopathy may have a higher yield justifying the cost. The association of the various grades of retinopathy with neuropathy can guide the timing for carrying out these tests. This will help in instituting tighter control measures at an early stage to prevent complications of peripheral neuropathy. Therefore, this study was carried out for the detection of peripheral neuropathy among diabetics who had developed retinopathy but were undiagnosed and asymptomatic for peripheral neuropathy. This study also attempted to assess the other risk factors for neuropathy in this population subgroup and look for an association between the various severity grades of retinopathy and peripheral neuropathy.

Methods

The study was done in a tertiary care multispecialty hospital with subjects being sampled from those reporting to the outpatient retina clinic of the Department of Ophthalmology between November 2014 and September 2016, by systematic random sampling. The study was carried out as per current guidelines of the Helsinki declaration. Institutional ethical committee clearance was taken prior to starting the study 19 Nov 2013. Patients with diabetic retinopathy of any grade and asymptomatic for peripheral neuropathy were included in the study. Retinopathy grading was done as per the Early Treatment of Diabetic Retinopathy (ETDRS) study criteria. Cases with coexistent retinopathy of cause other than diabetes, previous history of cerebrovascular accident, diagnosed neuropathy, peripheral vascular disease, and anemia were excluded from the study. A sample size of 234 was calculated taking an estimated prevalence of neuropathy of 15% among diabetics. For diagnosis and grading of diabetic retinopathy, all the enrolled patients underwent full ophthalmic examination including vision, slit-lamp examination, fundus biomicroscopy with 90 diopter lens, indirect ophthalmoscopy, color fundus photography, fundus fluorescein angiography, and optical coherence tomography. Best corrected vision was recorded by the ETDRS chart and vision recorded in Log MAR units. Informed consent was taken from all the patients and all of them also underwent blood and urine tests as a part of the treatment protocol for diabetic retinopathy including blood hemoglobin, urea, creatinine, lipid profile, glycosylated hemoglobin, and urine routine and microscopic examination. Nerve conduction studies were done at the Department of Neurology using Cadwell machine using Sierra wave software at surface temperature of 37.5°C and ambient temperature of 20°C to 24°C using surface electrodes. Motor and sensory nerves of both lower limbs were tested, peroneal and tibial nerve for motor and sural nerve for sensory. Sural nerve was tested with electrodes at the calf and lateral malleolus. For peroneal nerves, electrodes were placed at the head of fibula and ankle and for tibial nerve, near knee and ankle. The results were documented as neuropathy present or absent, sensory only, sensory and motor both, or motor only, based on the reference values for the lab. Data analysis was done using SPSS version 20. *P* value of 0.05 was taken as statistical significance. The Chi-square test was used for dichotomous qualitative data and unpaired t-test for quantitative data. The variables found to have significant association with neuropathy were then subjected to logistic regression analysis. Odds ratio and 95% confidence interval was calculated for those variables showing significant association with neuropathy after logistic regression analysis.

Results

A total of 234 patients were enrolled in the study and all of them underwent full ophthalmology evaluation and nerve conduction studies as per the study protocol. The demographic profile and other characteristics are listed in Table 1. The mean age was 59.12 years with a male preponderance. The majority were type 2 diabetic (90%) on oral hypoglycemic drugs with an average duration of 7.51 years since diagnosis. Current HbA1C levels indicated poor control (HbA1C >7) in 66% of the patients as compared to 34% with good control (HbA1C <7). Proliferative diabetic retinopathy (PDR) accounted for the largest chunk (35.9%) as compared to mild, moderate, and severe and very severe nonproliferative diabetic retinopathy (NPDR). The overall prevalence of neuropathy was 75.6% with the majority having combined sensory and motor neuropathy (58.54%) as opposed to only sensory neuropathy (17.1%). The prevalence of both sensory and combined neuropathy was seen to increase progressively with increase in severity of retinopathy [Figure 1]. Duration of diabetes, HbA1C levels above 7, gender, and severity grades of retinopathy showed a significant association with the presence of retinopathy on bivariate analysis [Table 2]. When these risk factors were subjected to multivariate logistics regression analysis, gender, duration, and severity grades of diabetes were significantly associated with retinopathy, whereas the association with Hb A1C was not found to be significant [Table 3]. Females were found to be less likely to have neuropathy as compared to males with an odds ratio of 0.471. Duration was significantly

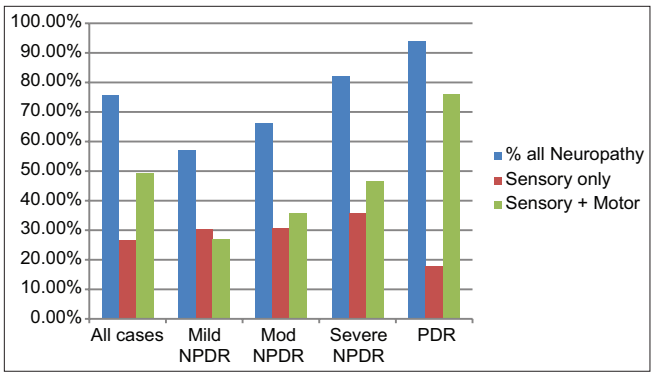

Figure 1: Prevalence of peripheral neuropathy in % in various grades of retinopathy

Table 1: Demographics of study sample in terms of age, gender, type of diabetes, treatment, duration and HbA1C levels

n=234		Mean and SD	Total Numbers	Percentage
Age*		59.12±8.43		
Duration in years*		7.51±5.61		
Hemoglobin (mg/dl)		12.88±1.67		
Blood Sugar F (mg%)		133.12±59.29		
Blood Sugar PP (mg%)		195.77±77.62		
Blood Urea (mg %)		32.13±10.98		
Blood Creatinine (mg %)		1.1±0.33		
Gender(M/F)			151/83	65%/35%
Type 1			24	10%
Type 2			210	90%
Oral Hypoglycemic (OHA)			183	78.2%
Insulin only			18	7.7%
Insulin and OHA both			24	9.8%
Alternative medicine (ayurvedic)			09	4.3%
Hb A1C <7			155	66.2%
Hb A1C >7			79	33.8%
Retinopathy Grade	Mild NPDR		63	26.9%
	Moderate NPDR		59	25.2%
	Severe and Very Severe NPDR		28	12%
	PDR		84	35.9%
Neuropathy	Total		177	75.6%
	Sensory Only		40	17.1%
	Sensory + Motor		137	58.54 %

Hb A1C: Hemoglobin A1C (Glycosylated Hemoglobin). SD: Standard deviation

Table 2: Distribution of neuropathy in relation to age, gender, duration, retinopathy grades, Hb A1C levels, and presence of nephropathy

	Neuropathy Present	Neuropathy Absent	Neuropathy % Group wise	Significance
Age: 60 years and above	110	22	83.3%	*P*=0.125
<60 years	67	35	65.7%	
Gender: Males	122	30	80.3 %	*P*=0.03
Females	55	27	67%	
Duration ≥10	147	08	94.8%	*P*=0.00
<10 years	30	49	38%	
HbA1C ≥7	126	29	81.3%	*P*=0.005
<7	51	28	64.6%	
Nephropathy (abnormal urea/creatinine): Present	22	14	61%	*P*=0.07
Absent	155	43	78.3%	
Grades of Retinopathy: PDR	79	5	94%	*P*=0.00
Severe and very Severe NPDR	23	5	82.1%	
Moderate NPDR	39	20	66.1%	
Mild NPDR	36	27	57.1%	
CSME	25	50	50%	

PDR: Proliferative diabetic retinopathy, NPDR: Nonproliferative diabetic retinopathy, CSME: Clinically significant macular edema

and positively associated with neuropathy (OR = 1.13, 95% CI = 1.02–1.24; *P* = 0.012); moderate NPDR (OR = 5.60, *P* = 0.002), severe and very severe NPDR (OR = 5.8, *P* = 0.041), and PDR cases (OR = 16.05, *P* = 0.000) were significantly at higher risk of having neuropathy as compared to mild NPDR.

Discussion

Retinopathy, nephropathy, and neuropathy are the comorbidities most commonly found in various population surveys on diabetics.[16,17] In this study, we have evaluated the prevalence of subclinical neuropathy and the associated risk factors among diabetics with various grades of retinopathy. To the best of our knowledge, this is the largest study in this particular subgroup. Our study population consisted predominantly of type 2 diabetics, which reflects the higher prevalence of type 2 diabetics across diabetic care clinics in India.[18] The result of this study highlights the much higher prevalence of peripheral neuropathy in the presence of diabetic retinopathy than that reported in population studies, among patients who were asymptomatic for neuropathy. A higher prevalence of neuropathy in our studies can also be attributed to the

Table 3: Risk factors for neuropathy following logistic regression analysis

Risk Factor	Odds Ratio	95% C.I. for Odds ratio		Significance
		Lower	Upper	
Gender Female	0.471	0.048	0.994	*P*=0.048
Duration	1.131	0.012	1.245	*P*=0.012
Retinopathy Grades				
Mild NPDR	1.123	0.841	3.476	*P*=0.841
Moderate NPDR	5.608	0.002	17.042	*P*=0.002
Severe and Very Severe NPDR	5.803	0.041	31.385	*P*=0.041
PDR	16.508	0.000	68.602	*P*=0.000
CSME	6.873	0.719	65.680	*P*=0.094
HbA1C	1.275	0.530	2.724	*P*=0.530

CI: Confidence limit, NPDR: Nonproliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, CSME: Clinically significant macular edema

diagnosis of neuropathy using nerve conduction. In the study by Venkatesh *et al.*[19] on patients with various grades of retinopathy, a higher yield was seen with nerve conduction as compared to clinical tests. An increased prevalence of neuropathy with increasing severity of retinopathy was seen in that study with a significant association with the presence of clinically significant macular edema (CSME). Although our study showed an increasing prevalence with increasing grades of retinopathy, statistically significant for moderate NPDR or worse, we did not see a significant association independently with CSME alone as noted by Venkatesh *et al.* Duration of diabetes was a significant determinant for neuropathy in this study similar to that reported by Feldman *et al.*,[20] Gill *et al.*,[21] and Ashok *et al.*[22] The role of tight control of hyperglycemia in preventing or delaying neuropathy has been well documented in various trials.[23-25] However, no significant association was seen between HbA1c levels and neuropathy in this study, probably because we have taken only the latest values and long-term average HBA1c measurements were not compared.[26] The association of neuropathy with male gender as seen in this study has been reported by several other studies as well.[24,27,28] This has been attributed to various factors such as health-seeking behavior, adherence to interventions and medications, smoking habit, obesity, etc., Since all of these factors were not matched or ruled out in our study, their role in influencing the association of male gender and neuropathy could not be assessed. Sensory neuropathy is usually the earliest to develop as reported in various epidemiological studies.[29,30] The same is reflected in the higher proportion of sensory only neuropathy seen in this study among those with milder grades of retinopathy as compared to combined motor and sensory neuropathy in the higher grades.

The primary care physician is usually the first point of contact for newly detected diabetic patients as well as patients with several years of disease. Hence, the primary care physician must be made aware of the importance of early screening for neuropathy and especially so in a patient with known severe retinopathy. The ADA recommends that patients with type 1 diabetes for 5 or more years and all patients with type 2 diabetes should be assessed annually for distal symmetric polyneuropathy using medical history and simple clinical tests.[31] Beyond this, some patients may not notice or be forthcoming with history of diabetic peripheral neuropathy and its detection may be missed on office clinical tests. With this study, the authors emphasize on the need for referring a patient with known diabetic retinopathy for more sensitive tests like nerve conduction studies (NCS) so as to detect preclinical neuropathy earlier.

To summarize, male gender, longer duration of diabetes, and severity of retinopathy are important risk factors for peripheral neuropathy. Severity of diabetic retinopathy is a marker for peripheral neuropathy which may be asymptomatic. It is suggested that such cases should be referred early for neurological evaluation and nerve conduction studies. A tertiary care setting with a bias toward more severe cases of retinopathy is a limitation of this study. A larger study is suggested with the sample drawn from population of diabetics seen at the primary care level.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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