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Original Research Article

Height is a risk factor for development of peripheral insensate neuropathy

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ABSTRACT

Background: Peripheral insensate neuropathy is one of the most common and forms of peripheral neuropathy. It is a preeminent cause for disability, foot ulcers, deformity and amputations in individuals who are at risk.
Methods: A study was conducted in Mahatma Gandhi Medical College & Research Institute, Pondicherry, India in the year 2017-18, which included examination of 760 people of more than 30 years of age by random sampling method who was attending the outpatient clinic. The Semmes Weinstein monofilament was adopted to ascertain the presence of peripheral insensate neuropathy.
Results: In present study, the prevalence of peripheral insensate neuropathy was 3.2%. As the height increased, the prevalence of peripheral insensate neuropathy increased, regardless of other independent risk factors like diabetes, hypertension, etc. The risk of the peripheral insensate neuropathy increases at a height of >171.5cm in males and at a height of >164.5cm in females.
Conclusions: The authors confirm that body height is a significant and independent risk factor for peripheral insensate neuropathy, regardless of co-morbidities. Height as a guide, helps the health care professionals in identifying the people who are at risk for peripheral insensate neuropathy.

Keywords: Diabetes Mellitus, Height, Peripheral insensate neuropathy, Peripheral neuropathy

INTRODUCTION

Peripheral insensate neuropathy (PIN) is defined as presence of one or more insensate areas.[1,2] PIN is a well-acknowledged problem and numerous determinants are associated with it like age, gender, race, glycemic control, malnutrition, toxins, drugs, alcohol, etc.[1,3,4]

Peripheral neuropathy affects 2-8% of adults, with an increasing incidence increase in age.[5] It is an incapacitating complication often seen in diabetics, because of its potentiality to cause lower extremity ulceration, deformation and amputation.[6] With early detection, proper history and focused laboratory testing, we can identify the underlying cause in ~75% of the cases and prevent morbid and expensive complications.[7-9]

Height is a valuable and useful predictor of PIN. As the height increases, the length of the nerve fiber also increases, so the surface area of axons available for toxin exposure and neuronal injury is more. The risk of PIN increases with increase in body height. Various studies have proven the interrelationship of body height wand peripheral neuropathy among diabetics.[1-3,10]

It is still obscure if there is any specific threshold in the affiliation of height and the risk for PIN in the general Indian population.

Early screening of PIN by health care personnel, tight glycemic control among diabetics, cessation of alcohol and smoking, correction of nutritional deficiencies, avoiding toxins and drugs and other preventive care are considered as key public health strategies against costly foot complications.[7,8]

A simple device, the Semmes Weinstein monofilament pf 5.07/10 gm is recommended by International Diabetes Federation, American Diabetes Association and World Health Organization for screening of peripheral neuropathy by healthcare personnel at all levels of care.[8] Previous studies have shown that presence of one or more insensate area to be highly predictive of ulcer formation and the monofilament has been found to have high sensitivity (~85%) and specificity (~80%) for development of ulcers and deformities.[11-13]

The association of body height and peripheral neuropathy has not been thoroughly investigated in the Indian population; there has been only one previous study that has concluded height as an independent risk factor.[2] Thus, this needs further exploration in the Indian context and a threshold height for screening needs to be settled upon.

METHODS

A cross sectional study was conducted in Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth University, Puducherry, India in the years 2017-2018, which included an examination of 760 people, with ages >30 years by random sampling, who attended the outpatient department. Informed consent was taken from the individuals and so was an institutional clearance from Mahatma Gandhi Medical College and Research Institute Sri Balaji Vidyapeeth, Puducherry, India.

Inclusion criteria

- People with age more than 30 years.

Exclusion criteria

- People with foot ulcers,
- People with calluses on the feet,
- People with Age <30 years.

Methodology

A detailed history was taken, with appropriate attention to sensory symptoms of neuropathy, drug ingestion, toxin exposure, diabetic and hypertensive status, smoking and alcohol consumption. A detailed examination was done, with emphasis on height and weight.

Individuals' blood was taken and was measured for complete blood count, fasting blood glucose, post-prandial blood glucose and glycosylated hemoglobin with their consent.

Peripheral insensate neuropathy assessment

The semmes weinstein monofilament of 5.07/10 gm force was used on the feet of patients while their eyes were kept closed.[11] The sensation was checked at 3 sites on the individual feet (Figure 1).

- The plantar hallux.
- The plantar 1st metatarsal head.
- The plantar 5th metatarsal head.

The filament was applied at the specified sites (Figure 1) until it buckled. The site was considered insensate if there were:

- Two incorrect responses.
- Two responses which were ambiguous.
- One incorrect response and one ambiguous response.

The sites were tested in a random order. PIN was marked as present if there were one or more insensate areas.

The parameters which were analyzed were:Hypertension ((+)/(-)), Diabetes ((+)/(-)), Consumption of alcohol. ((+)/(-)), Smoker ((+)/(-)), Height (quartiles) in cms (<151(+)/(-), 151-165(+)/(-), 166-170(+)/(-), >171(+)/(-)), BMI (<18.5(+)/(-), 18.6-24.9(+)/(-), 25-29.9(+)/(-),>30(+)/(-)), Anemia ((+)/(-)), Duration of Diabetes (> 7 years(+)/(-),< 7 years(+)/(-)), Duration of hypertension (>7 years(+)/(-)<7 years(+)/(-)), HbA1C (<6(+)/(-), 6-6.9(+)/(-), 7-7.9 (+)/(-), >8(+)/(-)). The data analysis was carried out by using the Chi square test, logistic regression analysis and the SPSS software, version 17.0. A 'p value' of <0.05 was considered as significant.

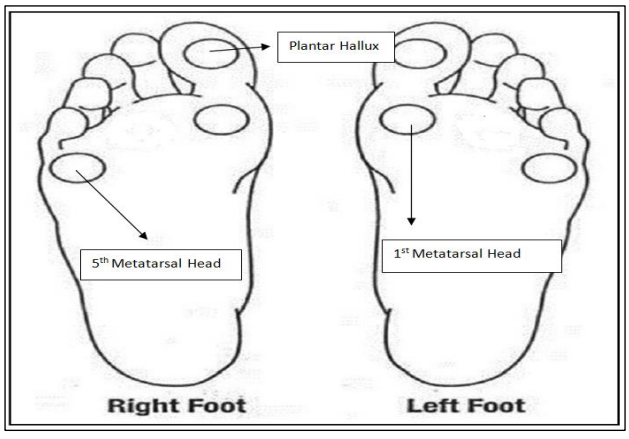

Figure 1: Sites on the foot for monofilment test.[2]

RESULTS

This study included the examination of 760 patients who attended the outpatient department, where the mean height was 164.9cm. The prevalence of PIN was 3.2% (4.7% in males and 2.5% in females) (Table 1). The

height which was adjusted for the gender analysis was not found to be significant (Figure 2).

Table 1: Group variables.

Variables		Numbers (percentage)
Gender	Male	233 (30.7%)
	Female	527 (69.3%)
Age	31-40 years	248 (32.6%)
	41-50 years	220 (29%)
	51-60 years	176 (23.2%)
	61-70 years	77 (10.1%)
	>70 years	39 (5.2%)
Anemia	Present	55 (7.4%)
	Absent	705 (92.6%)
DM	Present	168 (22.1%)
	Absent	592 (77.9%)
HTN	Present	119 (15.7%)
	Absent	641 (84.3%)
BMI	Lean	26 (3.4%)
	Normal	253 (33.2%)
	Overweight	331 (43.5%)
	Obese	150 (19.7%)
Alcohol	Present	46 (6.1%)
	Absent	715 (93.9%)
Smoking	Present	30 (3.9%)
	Absent	730 (96.9%)
Height (Quartiles)	0-25%	197 (25.9%)
	25-50%	211 (27.8%)
	50-75%	174 (22.9%)
	75-100%	178 (23.4%)

The people with hypertension and diabetes were found be at a higher risk for PIN. The prevalence of PIN among the hypertensive group was 8.5% as compared to 5.4% among the diabetics (Figure 3, 4).

The duration of hypertension and diabetes was directly proportional to the prevalence PIN; this was found to be statistically significant. Glycemic control was risk factor with higher HbA1c levels correlating with higher frequency of PIN, but this was not found to be statistically significant. PIN prevalence increases as the age advances, irrespective of the gender (<40years-1.6%,>70years -5.1%). Among the people, PIN was found to be highest between the ages of 60-70 years (7.8%) (Figure 5).

The mean height was 168.1 cm among men and it was 157.6cm among women. For analysis, authors segregated the people into quartiles to find relationship between height and PIN, regardless of gender, age, diabetic and the hypertensive statuses, anemia, BMI, alcohol intake and smoking. Authors found that the threshold of prevalence of PIN increased with increase in height, as seen in the fourth quartile (p=0.002) (Figure 6).

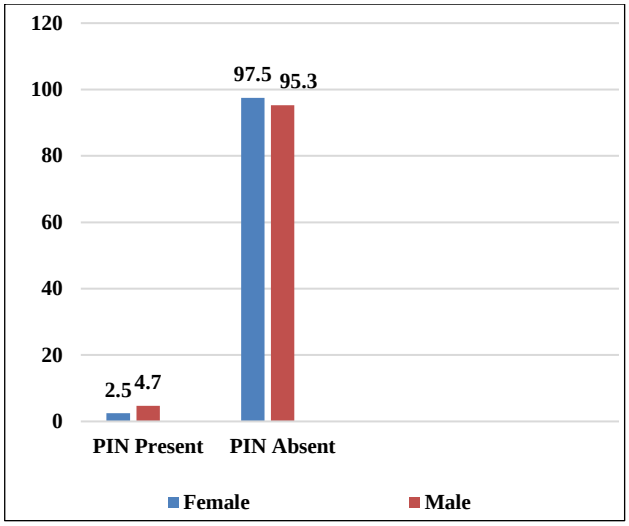

Figure 2: Association of pin with gender.

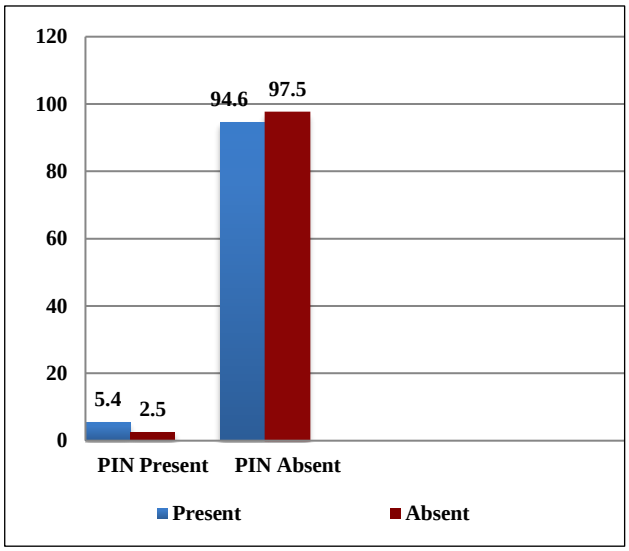

Figure 3: Association of pin with diabetes.

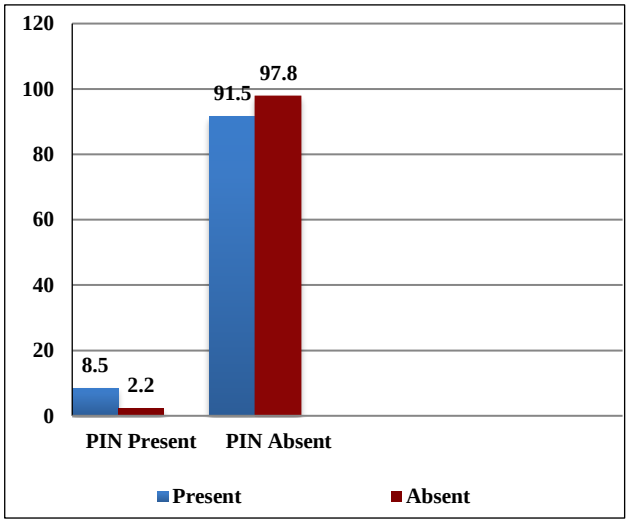

Figure 4: Association of pin with hypertension.

Table 2: Distribution of variables in height quartiles

Variables		0-25% PIN YES	0-25% PIN NO	P value	25-50% PIN YES	25-50% PIN NO	P value	50-75% PIN YES	50-75% PIN NO		75-100% PIN YES	75-100% PIN NO	P Value	Total
Gender	Female	0 0%	53 0.1%	0.39	1 0.2%	153 29%	0.46	3 0.6%	152 28.8%	<0.001	10 1.9%	155 29.4%	0.02	527 (100)
	Male	2 0.9%	142 60.9%		1 0.4%	57 24.5%		4 1.7%	15 6.4%		2 0.9%	10 4.3%		233 (100)
DM	Present	1 0.6%	43 25.6%	0.4	0 0%	54 32.1%	0.6	3 1.8%	36 21.4%	0.19	5 3%	26 15.5%	0.05	168 (100)
	Absent	1 0.2%	152 25.7%		2 0.3%	155 26.2%		4 0.7%	131 22.1%		8 1.4%	139 23.5%		592 (100)
HTN	Present	2 1.7%	35 29.7%	0.03	0 0%	33 28%	0.7	2 1.7%	20 16.9%	0.2	6 5.1%	20 16.9%	0.005	118 (100)
	Absent	0 0%	160 25%		2 0.3%	175 27.3%		5 0.08%	147 22.9%		7 1.1%	145 22.6%		641 (100)
BNI	Lean	0 0%	2 7.7%	0.8	0 0%	16 61.5%	0.9	0 0%	3 11.5%	0.87	0 0%	5 19.2%	0.7	26 (100)
	Normal	0 0%	61 24.1%		1 0.4%	64 25.3%		2 0.8%	61 24.1%		5 2%	59 23.3%		253 (100)
	Over-weight	1 0.3%	67 20.2%		1 0.3%	94 28.4%		3 0.9%	76 23%		8 2.4%	81 24.5%		331 (100)
	Obese	1 0.7%	65 43.3%		0 0%	35 23.3%		2 1.3%	27 18%		0 0%	20 13.3%		150 (100)

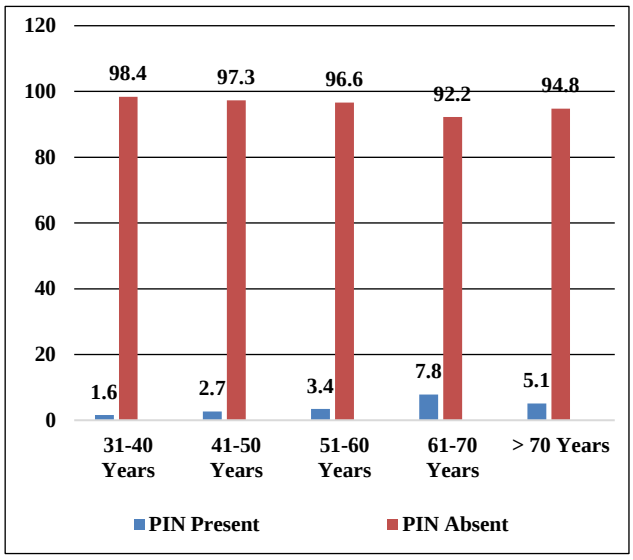

Figure 5: Association of pin with age.

As shown in (Table 2), author also found a similar association between the height and the PIN across the stratification of diabetes, the hypertension, gender and BMI. Authors accomplished this by arranging the individuals with known risk factors in quartiles of height; author found that the fourth quartile had more prevalence of PIN.

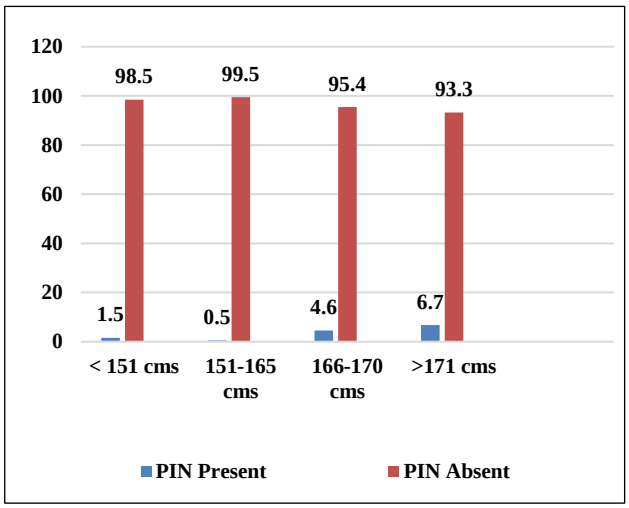

Figure 6: Association of pin with height (quartiles).

In the study population, the risk of PIN was significantly higher among males >171.5cm and among females, it was >167.5 cm.

In present study, author also found a statistically significant association between PIN and smoking and the alcohol consumption while we did not find a significant association between BMI and PIN.

The logistic regression analysis nullified the effect of individual variables on each other. Thus, present study showed that age, diabetes, hypertension, alcohol consumption, smoking and height (quartiles) were independent variables having significant correlations with PIN.

DISCUSSION

In this cross-sectional study, authors confirmed that PIN is associated with increasing age, diabetes, hypertension, alcohol consumption and smoking.[1,2] Authors also found that being tall and male was a similarly important risk factor.

The methodology for defining PIN (PIN) in the study was similar to the previous studies such as Cheng YJ et al, and Kote GGS et al, both of which attempted to standardize the definition of PIN.[1,2] As per the definition of PIN described in the method section, 3.2% of subjects had PIN. It was lesser in comparison to other studies which was probably due to difference in race and ethnicity like shown by Abbott CA et al.[1,2,14] The reason for the difference in rates between ethnic groups is unknown but height may be one of the factors as shown by Tseng et al, and Abbott CA et al.[14,15]

The prevalence of PIN in males was 4.7% as compared to females 2.5%. It is lower than previous studies like Cheng YJ et al, and Kote GS, where it was 16.2% and 9.7% vs. 9.4% and 7.6%.[1,2] But the height adjusted gender analysis showed no statistical significance (p=0.1), association of PIN with male gender. There was significant gender difference in present study compared to previous studies.[1,2,4,16] which have shown PIN being more prevalent in males. This is attributed to height as well as ethnicity.[1-3,17] The difference between the genders can also be explained on the basis of biomechanics of foot as seen in the study of Dinh et al.[18] In present study, gender was not a significant factor for development of PIN.

In present study the prevalence of PIN increases as the age advances (p=0.09). Prevalence roughly increased by 10% from 41-50 to 51-60 years, comparable to Gregg EW et al, and almost tripled in age group 61-70 years, however there was a drop in above 70 years age group, the reason is not known.[16] As compared to previous studies, the prevalence of PIN increases as the age advances irrespective of diabetic status. Attribution of increase in PIN with age may be because of decreased nerve fibers, reduction in nerve diameter and change in fiber membrane and conduction velocity as shown in the studies of Huang CR et al, and Chu NS et al.[19,20]

In present study, prevalence was more than twice as high for individuals with diagnosed diabetes (5.4%) as compared to those without diabetes (2.5%). It was comparable to previous studies such as Cheng YJ et al, and Kote GS et al.[1,2] PIN was more common in diabetics.[4,6,16,21–25]

The prevalence of PIN was more in individuals with longer duration of diabetes as compared to individuals with shorter duration. Individuals with higher HbA1C levels were also found to have higher frequency of peripheral neuropathy than individuals with tight glycemic control. These findings were similar to those seen in other studies.[16,24,26-28]

Hypertension was found to be significantly associated with prevalence of PIN in our study (p<0.001). Prevalence of PIN in hypertensive group was 8.5% as compared to 2.2% in non-hypertensive group, which was almost quadruple that of the non-hypertensive group. Studies have shown hypertension is one of the modifiable risk factors of PIN which play a significant role in prevalence of PIN as suggested in present study, due to both micro and macovascular complications that accompany hypertension.[24,29] The prevalence of PIN was more in patients with longer duration of hypertension than patients with shorter duration of hypertension.[30,31]

Very few studies have shown an association between BMI and PIN.[32] Present study, PIN was not associated with increasing BMI which was supported by a recent meta-analysis that also came to a similar conclusion.[33]

Height was found to be a significant, independent and effective predictor of PIN.[1–4,15,34,35] The individuals in the study were divided into quartiles based on their heights. The prevalence of PIN was 1.5% in the first quartile, 0.5% in the second quartile, 4.6% in the third quartile and 6.7% in the fourth quartile. The above data confirmed and established that PIN was associated with increase in height. This correlation was found to be statistically significant (p=0.002).

In present study to find out the significance of height as an important variable and to rule out the association of other variables like diabetes, hypertension, gender and BMI, Author distributed these variables with respect to height quartiles. Author found that height was an independent variable in causation of PIN.

The Indian average height in males is 164.5 cms and in females is 152 cms (Population date from Census of India, 2001). In present study, Author found average height to be 164.9 cms, with mean height for males being 168.1 cms and for females being 157.6 cms. Authors found that males above 171.5 cms were at a high risk for PIN and females who were above 161.5 cms and thus would like to propose them as thresholds for screening.

The present study was similar to previous studies like Cheng YJ et al, and Kote GS et al, where greater height was associated with increased PIN prevalence among people with and without diabetes (p=0.002).[1,2] In the two aforementioned studies prevalence of PIN was more

among people who were taller than 175.5 cms and 167 cms respectively.[1,2] However in present study, there was a sharp increase in PIN, in males after 171.5 cms and after 162.5 cms in females. This could probably be attributed to the demographic difference. It is implausible that height is a generic risk factor of peripheral nerve function, as seen with Barrenas et al.[36] Although, studies have confirmed that increasing height was associated with foot ulcers and lower extremity amputation.[37]

Exact pathogenesis of height and PIN is not known. There are various proposed hypotheses, first being increase in height is associated with increased nerve length and greater axonal surface area, hence there is greater risk of injury as shown Cheng YJ et al, and Polydefkis M et al.[1,38] Second being, greater the length of the nerve, prolonged time for complete recovery of injured nerve. Thirdly, as the height increases, the hydrostatic pressure in the lower limbs increases. In the elderly and diabetics, there is a loss of compensatory responses to large pressure changes in small blood vessels and thus, it is hypothesized that this will lead to PIN. And finally, the last conjecture states that larger skin thickness of the soles in taller individuals is linked to PIN. Height was not associated with painful neuropathy.[1,2,4,24]

The present study showed significant association between smoking and development of PIN which was similar to a recent meta-analysis.[39] Smoking was found to cause microvascular complications that may be the cause for PIN. Alcohol consumption was also significantly associated with PIN, which is similar to the findings of a recent meta-analysis conducted by Julian et al, the cause is postulated to be nutritional deficiency.[40]

Present study was a cross-sectional study and the sample size was not representative of the entire population. The duration of diabetes and hypertension specified in the study is not a true reflection of the duration of the illness. Since this was a cross-sectional study, authors were incapable of concluding the association between modifiable risk factors and development of PIN as a cause-effect association. Authors used the monofilament test to determine the presence of PIN, while this has decent sensitivity and specificity; nerve conduction studies have better accuracy.

CONCLUSION

Height is one of the independent risk factors for development of peripheral insensate neuropathy. Diabetes and hypertension are also found to be important independent risk factors. Body height will help heath care providers in identifying individuals who will require intensive neurological screening. We recommend individuals with height more than 171.5cm in males and 162.5cm in females to be screened annually for development of peripheral insensate neuropathy after the age of 30 years regardless of risk factors.

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