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Prevalence of Painful Diabetic Peripheral Neuropathy among Patients with Diabetes Attending a Tertiary Outpatient Diabetes Clinic in Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Authors EEY, CBN, OSE, ODO and BMO designed the study. Author EEY performed the statistical analysis. Authors EEY, CBN and OSE wrote the protocol and wrote the first draft of the manuscript. Authors CBN, BMO, ETU, CE and CHE managed the analyses of the study. Authors EEY and CBN managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine the prevalence of painful diabetic peripheral neuropathy (pDPN) and its associated risk factors using the *Douleur Neuropathique en 4* (DN4) questionnaire in a cohort of patients with diabetes attending a tertiary hospital in Nigeria.
Study Design: The study was a cross-sectional descriptive study.

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Place and Duration of Study: The study was conducted in the outpatient diabetes clinic of the University of Nigeria Teaching Hospital, which is a tertiary hospital located about 15 km outside Enugu. Enugu is a town in South East Nigeria. The study was conducted between June and August 2017.
Methodology: A systematic random sample of 1 in 4 diabetic patients attending the outpatient clinic were recruited and screened following informed consent. Socio-demographic data was collected and fasting blood glucose recorded. The DN4 questionnaire was administered and the total score calculated. A DN4 score of ≥4 was recorded as diagnostic of pDPN. Data collected was analyzed using SPSS V23.
Results: A total of 272 patients; (46.3%) males were recruited. Type 2 diabetes was present in 95.6% and 57.4% had hypertension. Poor glycemic control was present in 79.2% and 44.5% had pDPN. In addition, pDPN was more prevalent in those on insulin (*P* =.007, OR =1.96) and diabetes duration more than 10 years (*P* = .004, OR = 1.92) and was not significantly associated with age, gender, body mass index or glycemic control. Significant predictors of pDPN in the regression model were, treatment with insulin (*P* = .022, CI - 1.100 - 3.347) and diabetes duration greater than 10 years (*P* = 0.015, CI - 1.141 - 3.365).
Conclusion: pDPN was common in diabetic patients and associated with insulin use and diabetes duration > 10 years.

Keywords: Diabetic neuropathy; pain; DN4; Nigeria.

1. INTRODUCTION

Painful diabetic peripheral neuropathy (pDPN) - a common, predominantly chronic, complex and worrisome complication of diabetes mellitus (DM), whose symptoms and signs typically reside in the toes, feet and legs; affects a significant number of individuals with DM and impacts negatively on their quality of life [1,2]. Although the pathophysiology of pDPN is not yet fully elucidated, it is thought that an initial axonopathy of the affected sensory neurons gives rise to the hyperexcitability seen in these neurons due to some changes in gene expression and abnormal proliferation and misregulation of Na^+ and Ca^{2+} ion channels [3,4]. The complex nature of pDPN is supported by the fact that some individuals have been found to have mainly deafferentation of nerves i.e. freeing of the motor nerve from its sensory component and hence, loss of sensory function while some others have more of hypersensitivity of nerves in the presence of preserved nerve integrity [4]. The above differences may account for the different cluster of phenotypes seen as regards to signs and symptoms present in affected subjects.

Painful diabetic peripheral neuropathy, usually arises in an individual with background diabetic peripheral neuropathy (DPN), described as a symmetric sensori-motor polyneuropathy which may affect either small or large sensory fibers, with a predilection for the feet and later, hands, in a "stockings and gloves" distribution [5]. The polyneuropathy, which affects about one third to more than half of diabetic patients [1,6-7], is sequel to effects of long-standing hyperglycemia with its attendant adverse micro vascular changes, leading to nerve ischemia [8]. In addition to heightened abnormal oxidation and glycation end products; sorbitol and fructose accumulation all combine, to lead to direct nerve damage [8]. Clinically, pDPN tends to be described as burning, shooting or aching and may be accompanied by allodynia, hyperalgesia and numbness [9].

In recent years, well-validated, easy-to-use screening tools and protocols have been devised to help establish, with high levels of accuracy, individuals with pDPN and in this study we aimed to assess the presence of pDPN in a cross-section of out-patient subjects with diabetes using the *Douleur Neuropathique en 4* (DN4) questionnaire [10]. Our objectives were – to find out the prevalence of pDPN in the study population and to find out the risk factors associated with pDPN in these subjects.

2. MATERIALS AND METHODS

2.1 Study Site and Study Population

The study was carried out at the out-patient diabetes clinic of the University of Nigeria Teaching Hospital (UNTH) Enugu, Enugu State; a tertiary multi-specialty referral center which serves as the major referral hospital for the states in South-east Nigeria and some parts of South-south Nigeria.

2.2 Study Design

This cross-sectional study was carried out over 12 consecutive weeks among adult DM patients. The study was approved by the Health Research and Ethics Committee of the UNTH (NHREC/05/01/2008B-FWA00002458-1RB00002323) and is in compliance with the Helsinki Declaration of 1975, as revised in 2000.

The sample size was calculated using the formula [11];

$N = (Z)^2 (P (1 - P)/D^2)$. N= minimum sample size, P = prevalence of painful diabetic neuropathy, D is tolerable sampling error = 0.05, Z is standard deviation set at 1.96.

$Z = 1.96$, $P = 0.30$ [1]
$N = 322$.

Final sample size Nf = n/1+(n/N), where n is the finite population i.e. estimated as the number of new patients seen in the diabetic clinic over a year about 350.

Nf = 350/1 + (350/322), Nf = 169.
Allowing 10% drop out rate = 16
Final sample size 169 + 16 = 185.

Participants were randomly selected at each clinic day, from the attendance register through systematic random sampling of one in every fourth patient. Informed consent was obtained from the selected subjects, after they had received briefing regarding the study protocol from pre-trained attending physicians in the clinic. Subjects who refused consent were excluded from the study without any prejudices. A total of 305 subjects were enrolled for the study, however, only 272 of them had complete data at the end of the study.

2.3 Study Method

The *Douleur Neuropathique en 4* (DN4) questionnaire; a validated screening tool for identifying neuropathic pain in pDPN, with remarkably high sensitivity and specificity, [10] was administered on the subjects. The initial part of the DN4 questionnaire, involved interview questions which asked the patients information about the characteristics of the pain they felt and possible associated symptoms. The second part involved physical examination by the interviewer, using various modalities of tactile stimulus, with a view to eliciting a set of abnormal sensation in the area where subjects were experiencing the pain. This was accomplished by testing for fine touch using a ball of cotton and testing for prick using a sterile pin. The above two components, make up the simple, 10-interview-questions to which each subject either answers a “yes” or a “no”. Each “yes” scores 1 while a “no” scores zero. The total score was computed for each subject and recorded. Neuropathic pain was then said to be present if subject scored ≥ 4.

Other clinical parameters including weight, height, body mass index (BMI) and waist circumference were assessed. Weight was measured using a stadiometer calibrated to the nearest kg. Height was also measured with the same stadiometer and recorded to the nearest 0.1 m. Waist circumference was measured with a non-stretchable tape using the landmark of the midpoint between the highest margin of the iliac crest and the lowest margin of the rib cage. It was recorded to the nearest cm. Hypertension was recorded as present in subjects who were already on drug treatment for hypertension or who had an average of 2 blood pressure (BP) measurement of > 140 mmHg systolic and/or 90mmHg diastolic BP while sitting. Glycemic control was assessed using the average of the last 3 fasting blood glucose (FBG) readings of the subject. The American Diabetes Association (ADA) cut-off of FBG < 130 mg/dl was regarded as good control [12].

2.4 Statistical Analysis

Data was analyzed using the statistical package for social sciences (SPSS) version 22. Chi-square or student’s T-test as appropriate was used to determine differences between categorical and continuous variables. A p value < 0.05 was regarded as significant. Values with p < 0.2 on univariate analysis were entered into a logistic regression model to determine predictors of DN score ≥ 4.

3. RESULTS AND DISCUSSION

3.1 Subject Characteristics

There were 272 DM subjects of which 126 (46.3%) were males and 146 (53.7%) females. One hundred and thirty-seven subjects (50.4%) were aged between 45-64 years. Type 1 diabetes mellitus (T1DM) was present in 12 (4.4%) subjects, while 260 (95.6%) had Type 2 diabetes mellitus (T2DM). The mean BMI of all the subjects was 28.6 ± 11.4 kg/m^2. The mean systolic BP was 133.6 ± 20.9 mmHg, while the mean diastolic BP was 77.9 ± 12.1 mmHg.

Hypertension was present in 116 (42.6%) subjects while a fasting blood glucose level ≥ 130 mg/dl was recorded in 213 (79.2%) patients. Other features are as shown in Table 1.

3.2 Peripheral Neuropathy in the Study Subjects

Analysis of the individual symptoms of pDPN present in the subjects revealed that tingling sensation was present in 182 (66.9%) subjects while pain on brushing, (allodynia) was present in 17 (6.3%) subjects. Table 2 shows a breakdown of symptoms of pDPN present in the subjects.

The prevalence of pDPN in the study subjects was 44.5% (C.I = 38.5 - 50.4, S.E = 3.02). The distribution of the total DN4 scores of the patients is shown in Fig. 1.

Table 1. Clinical features of the study population

Parameter	Male n (%)	Female n (%)	Total n (%)	*P*
Age group (years)				.42
18 – 44	15 (11.9)	21 (14.3)	36 (13.2)	
45 – 64	60 (47.6)	77 (52.7)	137 (50.4)	
≥ 65	51 (40.5)	48 (33.0)	99 (36.4)	
BMI class (kg/m^2)				<.001*
Normal	54 (43.0)	34 (23.3)	88 (32.4)	
Overweight	52 (41.2)	52 (35.6)	104 (38.2)	
Obese	20 (15.8)	60 (41.1)	80 (29.4)	
Hypertension (n)				.39
Present	52 (41.3)	64 (43.8)	116 (42.6)	
Absent	74 (58.7)	82 (56.2)	156 (57.4)	
DM duration (years)				.64
< 10 years	85 (67.5)	86 (58.9)	171 (62.9)	
≥ 10 years	41 (32.5)	60 (41.1)	101 (37.1)	
Diabetes treatment (n)				
Diet	2 (1.6)	0 (0.0)	2 (0.7)	.04*
Oral Drugs	74 (58.7)	106 (72.6)	180 (66.2)	
Oral Drugs plus Insulin	21 (16.7)	18 (12.3)	39 (14.3)	
Insulin only	29 (23.0)	22 (15.1)	51 (18.8)	

**Significant values*

Table 2. Symptoms of peripheral neuropathy in the subjects

Symptoms	Males n = 126 n(%)	Females n = 146 n(%)	Total n = 272 n(%)	*P*
Tingling	80 (63.5)	102 (69.9)	110 (40.4)	.27
Burning	61 (48.4)	83 (56.8)	144(52.9)	.16
Numbness	59 (46.8)	78(53.4)	137(50.4)	.28
Pins/needles	55(43.7)	75(51.4)	130 (47.8)	.28
Hypersensitive to touch	35 (27.8)	38 (26.0)	73 (26.8)	.75
Hypersensitive to prick	33 (26.2)	32 (21.9)	65 (23.9)	.39
Electric shock-like sensation	19 (15.1)	27 (18.5)	46 (16.9)	.49
Itching	15 (11.9)	27 (1.4)	46 (16.9)	.47
Painful cold	17 (13.5)	17 (6.3)	34 (12.5)	.63
Brushing	8 (6.3)	9 (6.2)	17 (6.3)	.95

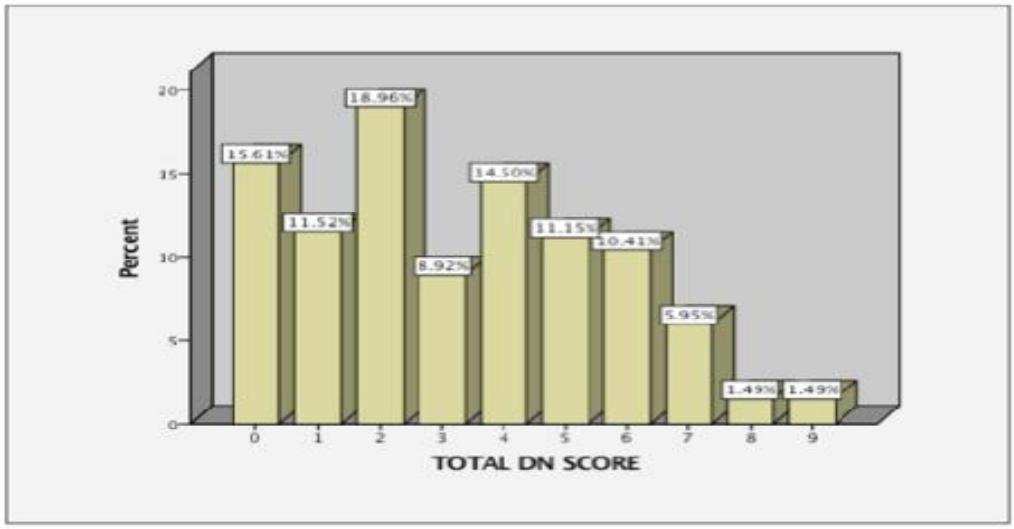

Fig. 1. Total DN scores in the study subjects

The clinical parameters of the subjects who had DN4 scores less than 4 were compared with those who had elevated scores, and the findings are as shown in Table 3.

Table 3. Categories of DN4 scores and clinical characteristics of the study subjects

	DN score < 4 N = 151 n (%)	**DN score ≥ 4 N = 121 n (%)**	***P***
Age (years)			
18-44	24 (66.7)	12 (33.3)	.29
45-64	76 (55.5)	61 (44.5)	
≥ 65	51 (51.5)	48 (48.5)	
Type of Diabetes			
Type 1	6 (50.0)	6 (50.0)	.46
Type 2	145(55.8)	115 (44.2)	
Gender			
Female	76 (52.1)	70 (47.9)	.22
Male	75 (59.5)	51 (40.5)	
Type of Treatment			
Oral	111 (61.0)	71 (39.0)	.007*
Insulin (± Oral)	40 (44.4)	50 (55.6)	
Diabetes Duration			
< 10 years	68 (67.3)	33 (32.7)	.004*
> 10 years	83 (48.5)	88 (51.5)	
Hypertension			
Present	84 (56.8)	64 (43.2)	.62
Absent	62 (53.4)	54 (46.6)	
BMI			
Normal	42 (66.2)	39 (33.8)	.73
Overweight	60 (57.7)	44 (42.3)	
Obese	44 (55.0)	36 (45.0)	
Fasting Blood Glucose (mg/dl)			
<130	31 (79.5)	8 (20.5)	.33
≥ 130	145 (68.1)	68 (31.9)	

**Significant values*

3.3 Predictors of Painful Neuropathy

Logistic regression was done, in a stepwise fashion, to determine the possible predictors of a high DN4 score. Variables which had a significance of $P < .20$ and below on univariate analysis were entered into the regression model. The variables entered into the model were age group of less than or greater than 65 years, glycemic control, diabetes duration greater or less than 10 years, gender and type of diabetes treatment (oral drugs or insulin). The findings are shown in Table 4.

3.4 Discussion

Painful diabetic peripheral neuropathy is a common, co-morbid condition in patients with DM and has been shown to reduce their quality of life [13,14]. Painful DPN is usually worse at night, and progressive if left untreated. Diabetic neuropathy on its own, is a risk factor for diabetic foot ulcer and the added presence of pDPN in a subject, may indicate a more advanced condition, increasing morbidity and mortality in such patients. This study set out to assess the prevalence of pDPN in patients with DM using a simple validated tool; the DN4 questionnaire, in a sample of diabetic patients attending an outpatient clinic in a tertiary hospital in Nigeria.

The study population had more females than males, reflecting the higher prevalence of diabetes in females in Nigeria, as reported in some community and hospital-based studies on DM [14,15]. The preponderance of middle-aged subjects in our study, is in line with the demographics of Type 2 DM worldwide, as T2DM was overwhelmingly more common in the study subjects than T1DM. More of the patients had had diabetes for less than 10 years, hence also accounting for the higher percentage of middle-aged subjects compared to the elderly. There was a high prevalence of hypertension in the subjects, as is commonly reported in studies among patients with diabetes [16,17], and majority were also either overweight or obese.

There was a high prevalence of pDPN among the subjects, with almost half (44.5%) of the study population being affected. The long duration of diabetes in the study subjects is a likely factor which could account for the high prevalence of pDPN in the patients. This high prevalence of pDPN, using the DN4 score, has also been reported in other studies [18,19]. A study conducted in Saudi Arabia, where the DN4 questionnaire was also utilized, a prevalence of 65.3% was reported for pDPN [18]. Similarly, in a larger study conducted among out-patient subjects with diabetes, in some select countries of the Middle East region; including Egypt, the Gulf States, Jordan and Lebanon, a prevalence of 53.7% was recorded for pDPN [19]. However, Jacovides et al. in their study in South Africa, recorded a lower prevalence of 30.3%, [1] while pDPN was prevalent in 14.4% of T2DM subjects in Korea [20,21]. The wide variations in prevalence may be accounted for, by the different diagnostic tools employed by the various researchers, in addition to possible differences in ethno-cultural pain perceptions, among the different populations cited [7,22].

In a study in Nnewi Nigeria, diabetic peripheral neuropathy was present in 69.3% of patients when the United Kingdom Screening Test (UKST) tool was applied, [23] although pDPN particularly, was not assessed. The prevalence of diabetic peripheral neuropathy using monofilament testing was reported to be as high as 59.2% in the Diabcare Nigeria study, [17] while Otu et al reported that 29.9% of patients with diabetic mellitus foot ulcer had underlying diabetic peripheral neuropathy, as measured using a 10 g monofilament [24]. Diabetic peripheral neuropathy was reported as the underlying risk factor for diabetic foot ulcer in

Table 4. Logistic regression showing predictors of a high DN score

Variables in the equation	B	S.E	Sig	Exp(B)	95% Confidence intervals for Exp (B)
Duration class (< 10 years, ≥ 10 years)	.673	5.94	.015*	1.959	1.141 - 3.365
Type of treatment (Oral/Insulin)	.652	5.271	.022*	1.919	1.100 - 3.347
Age group (< 65 years, ≥ 65 years)	.289	1.115	.291	1.335	0.781 - 2.284
Sex (Male/Female)	.413	2.431	.119	1.512	0.899 - 2.541

**Significant values*

57.6% of patients admitted over a 4 year period in a Nigerian tertiary hospital [25]. Although a good number of studies on diabetic peripheral neuropathy has been done in Nigeria, there is as yet, no study on pDPN reported in Nigeria to date.

In this study, although more female subjects had scores ≥4 compared to the males, the difference in pDPN prevalence was not significant. This may have been due to the fact that the males and females in our study had comparable age range and also had closely similar diabetes duration. Several studies have reported a higher prevalence of pDPN in females, with Jambart et al. recording a 1.27 higher risk of pDPN in females compared to males [19]. A higher female prevalence was also reported by Jacovides in South Africa, with females having a 1.5 times risk of pDPN as compared to males [1]. A nation-wide study of pDPN in T2DM Korean subjects, also revealed that the female gender was significantly associated with pDPN [20].

The most common symptom of pDPN in our study was tingling sensation, which was present in two-thirds of the subjects. Burning sensation was the second most common symptom, present in a little more than half of the study subjects; with numbness (coming a close third) reported in half of the subjects. In their study in the Middle East, Jambart et al reported burning sensation as the most common symptom, with tingling sensation as the third most frequent [19]. Symptoms of pDPN are often difficult to describe and include tingling, burning, numbness, electric shock-like sensation and other abnormal sensations. Many patients do not report their symptoms until the pain is severe. Tingling sensation however is easy to describe and thus was easy to report by the subjects.

The age groups of patients with neuropathy did not differ significantly from that of patients without neuropathy. Diabetic complications are expected to worsen with longer duration of diabetes and possibly, with increasing age. However, due to the varying age at diagnosis, this may not always be apparent as there may have been older patients who developed diabetes in their later years (in the sixth decade or greater, of their lives). However, with ageing, individuals expectedly, are more likely to have been exposed to other noxious factors that might affect the peripheral nerves adversely hence, a concomitant persistently raised blood glucose, may then precipitate neuropathy faster in such individuals. Jambart et al in their study reported that age ≥ 65 years was significantly associated with pDPN (OR 2.13) [19]. Jacovides in their study reported a significantly higher risk of pDPN in subjects aged 50 -64 years [1]. Pai Y et al. and Kim SS et al. also found older age to be significantly associated with pDPN among Taiwanese and Korean adults respectively, who had T2DM [26,20]. The majority of our patients were aged 40 - 64 years, and this may have accounted for the reason why age was not significantly associated with pDPN in our study.

Painful diabetic peripheral neuropathy was more common in the subjects who had had diabetes for more than 10 years, compared to those who had had diabetes for less than 10 years (P = 0.015, OR = 1.9). In addition, a diabetes duration of more than 10 years was a significant predictor of pDPN in the regression model. This was expected, and has been reported by other authors, [18-20] with DM duration greater than 10 years, consistently emerging as a significant risk factor for pDPN. In a study in North Western Nigeria, longer duration of diabetes was a significant independent predictor of neuropathy (OR 5.83) [27]. A longer duration of diabetes is likely to result in a greater incidence of complications and this was demonstrated in this study. Insulin use was also significantly associated with the presence of pDPN in the subjects (P = 0.022, OR = 1.9). This was an expected finding as insulin use in type 2 diabetes is associated with long duration of illness and poor glycemic control most likely due to beta cell exhaustion.

There was no significant difference between the BMI of the patients with pDPN and those without pDPN. Obesity is a common feature and risk factor for type 2 diabetes, but has not been directly associated with increased risk of complications. Obesity however may worsen insulin resistance in patients and its reduction usually improves glycaemic control. Reports on the relationship between obesity and the presence of pDPN are varied. In the study in patients in the Middle East, [18] a BMI > 30 kg/m^2 was associated with a 2.43 odds of developing pDPN, while a multi-center study in Saudi Arabia, which reported a prevalence rate of 35% for pDPN, [28] did not find any significant relationship between BMI and the presence of pDPN in their study population. Spallone et al. also reported that obesity was significantly associated with pDPN in their study [29]. However, there was a much higher prevalence of

overweight and obese subjects in the Middle East study, compared to those in the present study which may have accounted for these differences.

About half of the subjects had hypertension, which is a common co-morbid condition in DM. There was no difference in the hypertension prevalence of patients with pDPN and those without. This may have been due to the effect of hypertension treatment in the subjects as effective blood pressure control may have helped curtail the advancement of neuropathy in affected subjects. An earlier study had also reported no relationship between mean systolic or mean diastolic BP with neuropathy [28]. However, a few other studies have demonstrated a relationship between hypertension and painful neuropathy in patients with diabetes [18,20,30].

Painful diabetic peripheral neuropathy, one of the long-term consequences of poor glycemic control, is one of the chronic complications of diabetes mellitus. The fasting blood glucose of the subjects had a significant, though weak correlation with their DN4 scores ($r = 0.26$, $p < 0.001$) and same was also reported to be significantly associated with pDPN in a study among Korean adults with T2DM [20] However, when the patients in our study were classified into those with good glycemic control and those without, the DN4 scores did not differ significantly between them. In another study, there was no correlation between prevalence and advancement of sensorial neuropathy and current diabetes control in patients with long-term established diabetes [31]. High glycated hemoglobin (HbA_{1c}) levels, have been associated with pDPN [26,30]. However, it is debated whether high HbA_{1c} and hypertension, which are all known complications of DM can actually be said to be factors contributing to pDPN risk or onset, or simply co-existing factors [32].

4. CONCLUSION

Painful diabetic peripheral neuropathy was highly prevalent in the subjects and was associated with longer duration of diabetes and use of insulin for treatment. The major contributor to the presence of pDPN in the subjects, was a DM duration of more than 10 years. Hence, concerted efforts should be made to sensitize physicians to specifically seek out diagnostic symptoms of pDPN, especially in patients with long duration of DM, with a view to offering effective treatment and improving quality of life of the subjects. This is pertinent, as physicians tend to accord pDPN treatment a low priority, compared to other associated complications of diabetes; a view in discordance with that of affected subjects [33].

CONSENT

All authors declare that written informed consent was obtained from the study subjects before participation.

ETHICAL APPROVAL

Ethical approval for the study was obtained from the Ethical committee of the University of Nigeria Teaching Hospital Enugu with reference number - (NHREC/05/01/2008B-FWA00002458-1RB00002323).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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