A clinical and electrodiagnostic study of diabetic neuropathy at Jordan University Hospital

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ABSTRACT

Objectives: To study diabetic neuropathy (DN) at Jordan University Hospital (JUH) with the aim of assessing age/gender distribution, risk factors, and other diabetic microvascular complications, clinical manifestations, results of nerve conduction studies (NCS), and treatment modalities, and to compare these findings with those from Western and other Middle/Far Eastern literatures.

Methods: Among 562 patients with diabetes mellitus (DM) seen over a 2-year-period from January 2003 to January 2005, at the Diabetes center at Jordan University Hospital (JUH), 110 patients (10 DM type 1; 100 DM type 2) were studied retrospectively.

Results: The prevalence of DN was 20%. The mean age was 55.4 years (range 23-75), with 62 females and 48 males. The most common risk factors for DN were old age, long duration of DM, mean hemoglobin A_{1c}, and hypertension. Almost 50% of patients had additional retinopathy, renal involvement, or both. The most common clinical symptoms were distal numbness/paresthesiae in the limbs (60% of patients) and the neurological examination was normal in 2/3 of patients (only 20% had stocking hypoesthesia to pain and temperature and absent ankle jerks). The NCS showed an axonal neuropathy mainly affecting the lower limbs, especially sensory fibers (abnormal sural sensory action potential in 98% of patients). Anticonvulsants (carbamazepine and gabapentin) were used efficiently in 50% of patients as symptomatic treatment, while tricyclic antidepressants were used as add-on in only 23 patients, due to anticholinergic side effects.

Conclusion: In comparison with other studies, ours shows a lower prevalence of DN, similar age distribution with however, a predominance of females, similar risk factor profiles, clinical/NCS findings, and treatment modalities.

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Diabetic neuropathy (DN) is one of the major complications of diabetes mellitus (DM). It affects more than 50% of patients with a history of DM for more than 25 years.[1] At least 20% of diabetic patients have a neuropathic problem consisting of either pain, sensory discomfort, foot ulceration, or impotence, which represents a large clinical workload in any diabetes service.[2] Diabetic neuropathy is a chronic progressive disease accounting for considerable morbidity and reduced quality of life among patients with diabetes. One to 2% of the whole population in Western Societies may be affected.[3] It is predominantly a disease of the older diabetic population.[4] Estimates of the prevalence of DN range from 10-90% of the diabetic population, depending upon the criteria used to define neuropathy, and it occurs equally in type 1 and type 2 DM,[5] and its incidence approaches 50% in most diabetic patients.[6] Diabetic sensorimotor polyneuropathy remains the most common microvascular complication of both type 1 and type 2 diabetes,[7] accounting for up to 75% of diabetic neuropathies.[8] Up to 25% of individuals with diabetes develop painful DN, suffering spontaneous pain, allodynia, hyperalgesia, and other unpleasant symptoms.[9] Due to the importance of this problem and the scarcity of studies from the Middle East,[10] this study of 110 cases of DN observed at Jordan University Hospital (JUH) over a 2-year-period was carried out with the aim of assessing: 1) prevalence, 2) age and sex distribution, 3) risk factors and presence of other diabetic microvascular complications, 4) clinical manifestations and results of nerve conduction studies, and 5) treatment modalities. Our findings will be compared with those from Western and other Middle/Far Eastern literatures.

Methods. A retrospective study including patients with type I and II DM having symptoms of DN, confirmed by nerve conduction studies (NCS), referred to the Neurophysiology

department at JUH, Amman, Jordan, by diabetologists or neurologists during the period between January 2003 and January 2005. The JUH is a 530-bed tertiary care referral center serving a considerable proportion of the Jordanian population. Patients with chronic debilitating diseases were excluded. Diabetes mellitus was defined in accordance with the World Health Organization (WHO) criteria.[11] The patients' age and gender as well as the duration of DM, treatment modality, presence, or absence of hypertension, hyperlipidemia, smoking history, and family history of DM were recorded. Physical examination for the presence of clinical signs of other diabetic microvascular and macrovascular complications was performed. Hypertension was diagnosed if blood pressure was > 140/90 mm Hg. Plasma lipid measurement was performed after 12-14 hours of fasting, using the enzymatic colorimetric method. Low-density lipoprotein (LDL) was determined by the homogeneous turbimetric method. Hyperlipidemia was diagnosed if the total serum cholesterol was >5.7 mmol/L, LDL >4.93 mmol/L, and triglyceride >1.94 mmol/L. The degree of diabetic control was assessed by the average level of hemoglobin A_{1c} (HbA_{1c}) as measured over the last 2 years before the patients' inclusion in the study. Glycated hemoglobin was measured using ion-exchange chromatography, then the HbA_{1c} was calculated (normal range = 4.2-6.2%). Urine analysis for proteinuria and screening for micro albuminuria was performed on 3 occasions in all patients without overt proteinuria (normal up to 20 mg/L). Microalbuminuria was tested by a quantitative immunoturbimetric method. Nephropathy was diagnosed in the presence of proteinuria and a high level of blood urea and creatinine. Patients with suspected retinopathy had direct and indirect ophthalmoscopy as well as color fundus photography and fluorescein angiography of both eyes. Neuropathy was suspected clinically when the patient reported at least one of the following symptoms: pain, tingling, burning or loss of sensation, and when one of the following abnormalities was present: impaired or absent tendon reflexes, muscle wasting/trophic changes in feet, decreased vibratory sensation in patients less than 50 years old, decreased sensitivity to pinprick and temperature, impaired position sense, and it was confirmed by neurophysiological studies. Patients with clinical symptoms/signs of DN and normal NCS were excluded. Patients with isolated mononeuropathy or asymmetrical neuropathy were also not included in order to increase the accuracy of the diagnosis of peripheral neuropathy. None of the patients had additional lumbosacral radiculopathies. The NCS were carried out using a Medelec MS 60 (Vickers Healthcare company) machine. Techniques were performed with surface electrodes at a room temperature of 25°C. Studies were carried out in upper and lower limbs. The normal value of the sural sensory nerve action potential (SNAP) was obtained in our laboratory from 30 age-matched healthy controls, whereas the normal values of the other tests were taken according to Katirji.[12]

Sensory NCS. 1) Median SNAP was obtained by stimulation at the wrist with recording at digit 2 (antidromic technique) at a distance of 14 cm. Normal peak latency ≤ 3.8 ms, and normal amplitude ≥ 20 micro Volts. 2) Ulnar SNAP was obtained by stimulation at the wrist with recording at digit 5 at a distance of 14 cm. Normal peak latency ≤ 3.2 ms and normal amplitude ≥ 12 micro Volts. 3) Sural SNAP was obtained by stimulation at the calf with recording behind the lateral malleolus at a distance of 16 cm. Normal peak latency ≤ 4.4 ms, amplitude ≥ 5 micro Volts and sensory conduction velocity ≥ 40 m/s.

Motor NCS. 1) Median compound muscle action potential (CMAP) was obtained by stimulation at the wrist and recording at the abductor pollicis brevis at a distance of 8 cm, then stimulation at the elbow. Normal distal motor latency (DML) ≤ 4 ms, CMAP amplitude ≥ 5 mV and motor conduction velocity (MCV) ≥ 50 m/s. 2) Ulnar CMAP was obtained by stimulation at the wrist with recording at the abductor digiti minimi at a distance of 8 cm, then stimulation at the elbow. Normal DML ≤ 3.2 ms, CMAP amplitude ≥ 4 mV, and MCV ≥ 50 m/s. 3) Peroneal CMAP was obtained by stimulation at the ankle with recording at the extensor digitorum brevis at a distance of 8 cm, then stimulation below the fibular head. Normal DML ≤ 5.5 ms, CMAP amplitude ≥ 3 mV, and MCV ≥ 40 m/s. 4) Tibial CMAP was obtained by stimulation at the ankle with recording at the abductor hallucis at a distance of 8 cm, then stimulation at the popliteal fossa. Normal DML ≤ 6 ms, CMAP amplitude ≥ 4 mV, and MCV ≥ 40 m/s.

Due to evident clinical manifestations and NCS abnormalities, needle EMG was not deemed necessary. Treatment of DM was with oral hypoglycemic agents, insulin, or both. Symptomatic treatment of DN was initiated with anticonvulsants (carbamazepine [CBZ], gabapentin [Gb]) with eventual addition of tricyclic antidepressants. The response was appreciated on a visual analogue scale (VAS): 0=no pain; 10=very severe pain. Efficiency was reported if the patient noted subjective improvement and the VAS dropped from above 5 to below 5 on 2 consecutive visits separated by one month.

Results. Among 562 diabetics seen over a 2-year period at the Diabetes Center at JUH, DN was found in 110 patients with DM (10 type 1, and 100 type 2), thus indicating a prevalence of 20%. The age and sex distribution of the patients at the time of inclusion

in the study is shown in **Table 1**, which demonstrates that the majority (82/110 or 75%) were above the age of 50 years, the highest incidence (49 patients) being after the age of 59 years. The age range was 23-75 years, with a mean age of males of 53.4 years, and females of 51.4 years, and of all patients of 55.4 years. There were 62 females, and 48 males with a female/male ratio of 1.34. Risk factors for DN are also shown in **Table 1**, clearly demonstrating the highest incidence of DN in old people (75% >50 years). It also indicates that the majority (89/110 or 80%) had a DM duration longer than 5 years. The mean duration of DM in our patients was 11.3 years (range 3-31 years) and the mean duration of DM in males was 11.8 years, and in females was 8.8 years. The mean age of onset of DM = 46.2 years (range 20-72 years). The mean HbA_{1c} over the 2 years preceding DN was 8.68 in males, 7.35 in females, and 7.95 in all patients. Diabetic neuropathy was found in 61 patients with HbA_{1c} > 8, compared with 49 patients with HbA_{1c} < 8. The highest incidence of DN (79/110 or 72%) was in the HbA_{1c} range of 6.5-10. Seventy-seven patients (70%) had hypertension, 51 (46%) had hyperlipidemia, 22 were smokers, and 21 had a family history of DM. Regarding other microvascular complications, 54 patients (49%) had retinopathy, 60 patients (55%) had renal involvement (53 micro albuminuria and 7 nephropathy), 28 patients had a combination of neuropathy plus retinopathy plus microalbuminuria, while only 5 patients had a combination of neuropathy plus retinopathy plus nephropathy. The clinical manifestations of DN are shown in **Table 2**, which clearly demonstrates that the majority (67/110 or 60%) had numbness/paresthesiae distally, 39 patients in the upper and lower limbs, and 28 only in the lower limbs. Conspicuously the neurological examination was normal in 65 patients (60%) while the most frequent abnormal finding (23/110 or 20%) was a decreased sensation in a stocking-glove distribution with absent ankle jerks. An autonomic neuropathy was found on 25 occasions, 7 cardiovascular such as abnormal heart rate or postural hypotension, 14 erectile dysfunction, and 4 gastro intestinal (constipation in 2 and gastropathy in 2), some patients had more than one autonomic complication. The results of the NCS are shown in **Table 3**. Normal findings in sensory studies of median and ulnar nerves were noted in 44 and 59 patients, and motor studies of the same nerves were normal in 39 and 61 patients compared with normal findings found in only 2 patients for sural SNAP, 24 for peroneal CMAP and 20 for tibial CMAP, thus indicating a much higher rate of abnormalities in the lower limbs. An axonal neuropathy was found, especially in the lower limbs (decreased or absent sural SNAP, or decreased or absent peroneal and tibial CMAP ± slow SCV or MCV), more

Table 1 - Age and gender distribution/risk factors for diabetic neuropathy.

Risk factor	Gender		Total
	Male	Female	
Age (years)			
<40	7	4	11
40–49	12	5	17
50–59	11	22	33
>59	18	31	49
Total	**48**	**62**	**110**
DM duration (years)			
<5	6	15	21
5–10	17	18	35
10–15	10	12	22
>15	15	17	32
Total	**48**	**62**	**110**
Mean Hb A_{1C}[#]			
<6.5	3	3	6
6.5–8	13	30	43
8.1–10	15	21	36
10.1–12	12	6	18
>12	5	2	7
Total	**48**	**62**	**110**

DM - diabetes mellitus, #Mean hemoglobin A_{1c} over the 2 years preceding the neuropathy

Table 2 - Clinical manifestations of diabetic neuropathy.

Category	n	(%)
Symptoms		
Upper and lower limbs		
Numbness/paresthesiae*	39	(35)
Pain + numbness/paresthesiae	20	(19)
Lower limbs		
Numbness/paresthesiae	28	(25)
Pain + numbness/paresthesiae	18	(16)
Burning sensation	5	(5)
Total	**110**	**(100)**
Signs		
Normal exam	65	(60)
Abnormal exam		
↓sensation[#] with absent ankle jerks	23	(20)
↓sensation[#]	9	(8)
Absent ankle jerks	10	(9)
↓sensation with absent ankle jerks and bilateral foot drop	3	(3)
Total	**110**	**(100)**

#In a stocking-glove distribution, *of a distal distribution

Table 3 - Results of nerve conduction studies.

Limbs	Sensory (SNAP) (n)			Motor (n)		
Upper limbs	↑lat ↓SCV ±↓amp	NR	Normal	↑DML ±↓MCV ±↓CMAP	NR	Normal
Median	52	14	44	71		39
Ulnar	38	13	59	49		61
Lower limbs	↓amp ↑lat ↓SCV	NR	Normal	↓CMAP ±↓MCV	NR	Normal
Sural	60	48	2			
Peroneal				72	14	24
Tibial				81	9	20

Lat - distal peak latency, SCV - sensory conduction velocity, amp - amplitude, NR - not recordable, MCV - motor conduction velocity, CMAP - compound muscle action potential, SNAP - sensory nerve action potential, DML - distal motor latency, n - number of patients

commonly involving sensory fibers where abnormalities of sural SNAP were noted in 108 out of 110 patients or 98% compared with peroneal CMAP (86/110 or 78%) and tibial CMAP (90/110 or 82%). Regarding treatment, 55 patients were on oral hypoglycemic agents (OHA) and insulin, 41 on OHA, 10 on insulin and 4 on diet alone. Regarding symptomatic treatment for sensory symptoms, anticonvulsants were used efficiently in 55 patients (23 on CBZ, 17 on Gb, and 15 on a combination of both). Tricyclic antidepressants were added to CBZ, Gb, or both in only 23 patients.

Discussion. Several points emerge from this retrospective study of 110 patients with DN seen at JUH over a 2-year-period. Among the 562 patients with DM (100 type 1 and 10 type 2), the prevalence of DN was 20%, which is less than in other reports,[13-16] where the prevalence rates ranged from 32.3-60%. The exclusion of other concomitant debilitating diseases as well as diabetic mononeuropathies and asymmetrical neuropathies might be one reason for this low prevalence. The overwhelming predominance of type 2 DM compared to type 1 DM in our patients with DN (ratio 10/1) is not explainable. The mean age of our patients was 55.4 years, 75% being above the age of 50 years. This is in agreement with other reports.[10,17,18] There was a predominance of females in our study (62 females, 48 males, F/M ratio = 1.34), which is in accordance with Bashi,[10] (112 females, 89 males) but disagrees with others.[18,19]

Regarding risk factors, our study clearly indicates the highest incidence of DN in older people (75% above 50 years), thus showing that age was a risk factor. This is in full accordance with other reports.[14,18,20-22] Our study also demonstrates that long duration of DM was another risk factor for DN (mean duration of DM in our patients = 11.3 years, 80% >5 years), also in agreement with other studies.[14,15,20-25] According to Sangiorgio,[15] the duration of DM seems to be the most important risk factor and the relative risk of DN is increased for DM >20 years (p<0.0001). Pirart[1] also noted that the incidence of DN increased from 7.5% on admission to 50% at 25 years of follow up. In our study, DN was found in 61 patients with HbA_{1c} >8 compared with 49 patients with HbA_{1c}<8 thus showing a clear role of diabetic control in the occurrence of DN. This is in accordance with the Diabetes Control and Complication Trial (DCCT),[26] which showed that the maintenance of near-normal blood glucose levels and HbA_{1c} <7.5 with intensive insulin treatment reduced the incidence of neuropathy from 10% in the conventionally treated group to 3% in the intensively treated patients, a reduction of nearly 70% (p=0.006). Results of the UK prospective diabetes study group and Kumamoto trial[27,28] also supports the relationship between glycemic control and diabetic complications in patients with type 2 diabetes. The importance of a good glycemic control was also noted in other reports.[1,4,7,16,21,24,29-36] Huang[37] also concluded that hyperglycemia is the most important cause of electrophysiological progression in type 2 diabetic patients, and that a mean HbA_{1c} of >8.5 will result in a significant deterioration in electrophysiology. However, Parry[38] remarked that most studies of tight glycemic control do not address the complications of more intensive therapy, among them severe hypoglycemia, which can precipitate acute painful neuropathy. He also noticed that all studies have been confined to patients with mild neuropathy. Younger[39] also concluded that tight glycemic control does not prevent progression of neuropathy, especially in patients with severe motor and gait disability.

Despite a lower mean duration of DM in females (8.8 years) compared to males (11.8 years), and a lower mean HbA_{1c} in females (7.35) compared to males (8.68), yet the higher incidence of DN in our female patients indicates a possible higher susceptibility of females to diabetic neuropathy still unexplainable. This is in disagreement with ElShazly.[18] Seventy percent of our patients had hypertension demonstrating the importance of this risk factor. This is in accordance with other reports.[25] Only 46% of our patients had hyperlipidemia, and 22 were smokers thus indicating an insignificant role of these factors.

Regarding other microvascular complications, 49% of our patients had retinopathy and 55% had renal involvement mostly due to the severity of DM in our patients (61/110 or 56% with mean HbA_{1c} of >8). This is in full agreement with Bashi,[10] who noted a combination of neuropathy with retinopathy in 48% of patients and with nephropathy in 68.5% of patients, but disagrees with others.[40]

Regarding clinical manifestations, 60% of our patients had distal numbness and paresthesiae in the limbs, more in the lower limbs. This is in accordance with others.[38,41,42] Conspicuously, 60% of our patients had normal neurological examination, which concurs with Hong,[19] who noted that only one third of patients with symptoms will have clinical signs of DN. The most common sign of DN in our patients was a stocking hypoesthesia to pain and temperature, and absent ankle jerks, in accordance with others.[43] Concerning nerve conduction studies, our study demonstrates a higher incidence of abnormalities in the lower limbs compared to the upper limbs with an axonal type neuropathy affecting mainly the sensory fibers, where abnormalities of sural SNAP were noted in 98% of patients, thus correlating with the predominance of clinical sensory manifestations. These findings are in full agreement

with others.[43-45] The presence of an axonal type of neuropathy in our patients was also found by Abu Shakra,[46] who concluded that segmental demyelination and conduction block over long nerve segments are uncommon in DN and, if present, suggests that other causes for neuropathy in diabetic patients should be sought. According to Thomas,[47] a distal axonopathy of the dying-back type may represent the underlying pathogenetic basis of DN. Due to the scarcity of motor deficit, namely, foot drop, in our patients, needle EMG was not considered necessary for diagnosis of DN, which agrees with other reports.[43,48]

Regarding symptomatic treatment, anticonvulsants (CBZ, Gb, or both) were used efficiently in 50% of our patients, alone or as a combination. This is in accordance with other reports.[49] McQuay[50] concluded that for treating DN, anticonvulsants had a combined number needed to treat of 2.5 for effectiveness, 3.1 for adverse effects and 20 for severe effects (withdrawal from study). Tricyclic antidepressants (TCAs) were only used as add-on in 20% of our patients, is in agreement with others,[31,51] who concluded that TCAs have been well studied and shown to be effective but anticholinergic side effects may limit their usefulness.

In conclusion, our study shows: 1) a 20% prevalence of DN; 2) a predominance of females; 3) that risk factors for DN were old age, duration of DM, glycemic control, and hypertension; 4) that half of the patients had additional retinopathy or renal involvement; 5) a predominance of sensory symptoms mainly in the lower limbs; 6) an axonal neuropathy on NCS, mainly involving sensory fibers in the lower limbs and 7) an efficiency of anticonvulsants as symptomatic treatment.

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