

DIABETIC NEUROPATHY ASSESSED AT TWO TIME POINTS FIVE YEARS APART

Azra Alajbegovic¹, Salem Alajbegovic², Halima Resic³

Key words: diabetes mellitus type 1, diabetes mellitus type 2, diabetic neuropathy

SUMMARY

Patients with either type 1 or type 2 diabetes mellitus (DM) carry a risk of developing chronic diabetic complications. The aim of the study was to establish the prevalence of diabetic neuropathy in 300 patients with type 1 and 2 diabetes evaluated at two time points 5 years apart. The study included 300 patients with clinically diagnosed and laboratory verified diabetes. Initial examination, questionnaire and laboratory testing were performed in all patients in 1999 (type 1 diabetes 62 patients and type 2 diabetes 238 patients). Final examination, questionnaire and laboratory testing were performed in 2004 in 278 patients (type 1 diabetes 58 (20.9%) patients and type 2 diabetes 220 (79.1%) patients). Additional history taken on 2004 examination placed two female patients previously classified as type 2 diabetes to another specific diabetes type group. Twenty patients died in the period between March 31, 2000 and final examination taken

on February 1, 2004. In 1999, 51.1% of patients had diabetic neuropathy; in 2004, symptoms and signs of diabetic polyneuropathy were recorded in 84.2% of the same diabetic population. The increase in the number of patients with diabetic neuropathy recorded during the 5-year period was statistically significant. The average duration of diabetes was 13 years at initial examination and 18 years at final examination. In conclusion, diabetic neuropathy was significantly more common in 2004 than in 1999 in the same group of patients ($p < 0.01$). The risk of developing diabetic neuropathy increased with longer duration of diabetes ($p < 0.05$). Therefore, a more aggressive approach is necessary in the treatment of our diabetic patients, including education, physical activity and use of appropriate medication.

INTRODUCTION

Type 1 and type 2 diabetes patients carry a risk of developing chronic diabetic complications. These complications include diabetes specific microvascular (microangiopathy) and macrovascular (macroangiopathy) disease (1). Microangiopathic changes affect kidney glomeruli and small blood vessels in the eye retina and in nerves causing diabetic nephropathy, diabetic retinopathy and diabetic neuropathy (2). Diabetic symmetric distal neuropathy or diabetic

Corresponding author: Azra Alajbegovic, MD, University Department of Neurology, Sarajevo Clinical Center, 71000 Sarajevo, Bosnia and Herzegovina

E-mail: azra_alajbegovic@hotmail.com

polyneuropathy is the most common form of diabetic neuropathy and the leading cause of neuropathy in the United States. Complications include pain, loss of ambulation, and risk of amputation. Recognizing the typical pattern of presentation and risk factors for diabetic polyneuropathy is essential for making an accurate diagnosis and determining appropriate work-up and need for neurologic consultation. Intensive glucose control is the only therapy proven to prevent or slow down the progression of diabetic polyneuropathy. Supportive therapies including pain management and podiatric care can improve the patient quality of life and prevent chronic ulcerations (1,3).

Diabetic polyneuropathy is defined as metabolic, chronic axon myopathy of the sensorimotor type with a prevalence of around 70% in patients suffering from one of the types of DM. There are numerous mechanisms cited in the pathophysiology of polyneuropathy, such as ischemia caused by atherosclerosis or diabetic microangiopathy; accumulation of lipids in Schwann cells, which disrupts their normal metabolism; enzymatic disorders; and immune mediated mechanisms. Vascular hypothesis is most widely accepted; it assumes hyaline lysis and atherosclerosis of small blood vessels to cause nerve hypoxia and damage. Chronic hyperglycemia reduces the synthesis of acetylcholine. In case of insulin shortage in Schwann cells, there is an increase in the metabolic pathway of sorbitol synthesis from non-metabolized glucose, and in combination with fructose it stays in the intracellular space, thus directly causing swelling of Schwann cells. This state eventually leads to demyelination and axon destruction. Changed myelin acquires antigenic properties, which in turn trigger immune mechanisms (4).

There are multiple clinical manifestations which depend primarily on the nerves affected. The most common are sensitive symptoms (paresthesia), dysfunction of ocular muscles (semi ptosis or ptosis of eyelids, diplopia), and rarely motor symptoms (weakness, paralysis). Uncomfortable sensations of numbing, creepy crawlies and tingling, symmetrically distributed in distal parts develop, in the beginning

more prominent at night and later occurring in proximal parts of the legs also during the day. Cramps in the legs, rarely in the arms, are also a frequent complaint (5).

Neurological finding reveals disorder in surface and deep sensitivity, and lowered or, more frequently, extinguished Achilles reflex. With further progression of the disease, sensitivity disorder deteriorates to complete anesthesia of the foot and shin, and patellar reflex dies off.

The aim of this study was to assess the prevalence of diabetic neuropathy in a group of patients with type 1 and 2 diabetes followed up at two different time points 5 years apart. A closer aim was to determine difference in the occurrence of polyneuropathy between type 1 and type 2 diabetes according to diabetes type and mean age.

PATIENTS AND METHODS

The study included a group of 300 patients with previously diagnosed diabetes, confirmed clinically and by laboratory findings. Initial examination, questionnaire and planned laboratory testing were performed in all patients in 1999. There were 62 patients with type 1 diabetes and 238 patients with type 2 diabetes. Final examinations, questionnaire and laboratory testing were performed in 278 patients in 2004. There were 58 (20.9%) patients with type 1 patients and 220 (79.1%) patients with type 2 patients. According to additional history data collected in 2004, two female patients previously classified as type 2 patients were classified into another specific type of diabetes. Twenty patients died in the period between the initial and final testing.

Patients reported symptomatology of neuropathic pain with the characteristics of sensory neuropathy, in the form of paresthesias in a particular region involved in the pathophysiological basis of neuropathy. All patients with present symptomatology were referred to the neurologist for thorough examination. The counseling neurologist examined every patient according to the examination protocols and clinically made the diagnosis of polyneuropathy through an objective neurological examination, identifying the

Table 1. Mean diabetes duration according to sex and type of diabetes

Type of diabetes	Sex	Number of patients (n)	Mean diabetes duration in years (\bar{x})	Standard deviation (SD)	t-test of significance of sex differences in mean diabetes duration
1	Male	31	12.77	7.08	t=0.231; NS
	Female	27	12.33	7.40	
	Total	58	12.57	4.23	
2	Male	72	11.75 ^a	5.89	t=2.436; P<0.02
	Female	148	13.96 ^a	7.09	
	Total	220	13.24	6.80	
Total	Male	103	12.17 ^b	6.37	t=1.928; NS
	Female	175	13.76 ^b	7.14	
	Total	278	13.07	6.81	

^aP<0.02; ^bP<0.08

Table 2. Mean age of patients according to sex and type of diabetes

Type of diabetes	Sex	Number of patients (n)	Mean age in years (\bar{x})	Standard deviation (SD)	t-test of significance of sex differences in mean age
1	Male	31	43.00 ^a	11.85	t=0.097; NS
	Female	27	43.33 ^a	13.59	
	Total	58	43.16	12.69	
2	Male	72	60.08 ^{a,b}	8.24	t=2.653; P<0.01
	Female	148	63.22 ^b	8.22	
	Total	220	62.20	8.36	
Total	Male	103	54.94 ^b	12.30	t=2.080; P<0.01
	Female	175	60.15 ^b	16.94	
	Total	278	58.22	12.20	

^aP<0.001; ^bP<0.01

region affected by the neuropathic pain. We did not use pain scale since it is not used in routine neurology practice at our department.

RESULTS

Table 1 shows data on the mean diabetes duration expressed in years according to sex and diabetes type. On final assessment in 2004, there was no statistically significant sex difference according to the duration of diabetes in the group with type 1 diabetes, but it was recorded in the group with type 2 diabetes.

Table 2 shows mean age of patients and standard deviation in the study group as a whole and according to sex and type of diabetes. In total study population, patient age showed statistically significant sex difference in total study population and in the group of patients with type 2 diabetes (P<0.01 both). The difference between male and female patients with type 1 and type 2 diabetes according to mean age was not statistically significant.

Table 3 shows the presence of neuropathy according to sex and type of diabetes in total sample at both time points. During the 5-year time interval, 43.1% of patients with type 1 diabetes developed peripheral neuropathy, which had not been observed on initial examination, *versus* 30.9% of patients with type 2 diabetes that had developed diabetic polyneuropathy during the same time interval. Sex difference according to the development of polyneuropathy was statistically significant in both type 1 diabetes (P<0.05) and type 2 diabetes patients (P<0.01).

DISCUSSION

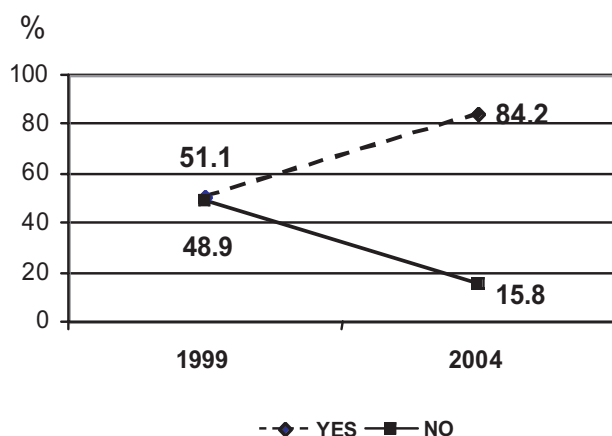
On initial examination in 1999, 51.1% of patients suffered from diabetic polyneuropathy, whereas 15.5% of patients showed no symptomatology of diabetic polyneuropathy. During the 5-year period, there was a statistically significant rate of polyneuropathy development, i.e. 33.5% of total study population. These patients were free from polyneuropathy

Table 3. Peripheral neuropathy according to sex and type of diabetes

Diabetes	Male		Female		Total	
	n	%	n	%	N	%
Type 1						
Patients free from peripheral neuropathy both in 1999 and 2004	9	29.0	10	37.0	19	32.8
Patients free from peripheral neuropathy in 1999 but with it in 2004	17	54.9 ^a	8	29.6 ^a	25 ^b	43.1
Patients with peripheral neuropathy both in 1999 and 2004	5	16.1	9	33.4	14 ^b	24.1
Total	31	100	27	100	58	100
Type 2						
Patients free from peripheral neuropathy both in 1999 and 2004	10	13.9	14	9.4	24	10.9
Patients free from peripheral neuropathy in 1999 but with it in 2004	30	41.7 ^a	38	25.7 ^a	68 ^b	30.9
Patients with peripheral neuropathy both in 1999 and 2004	32	44.4	95	64.2	127 ^b	57.7
Patients with peripheral neuropathy in 1999 but free from it in 2004	-	-	1	0.7	1	0.5
Total	72	100	148	100	220	100
Total types 1 and type 2 diabetes						
Patients free from peripheral neuropathy both in 1999 and 2004	19	18.5	24	13.7	43	15.5
Patients free from peripheral neuropathy in 1999 but with it in 2004	47	45.6 ^b	46	26.3 ^b	93	33.5
Patients with peripheral neuropathy both in 1999 and 2004	37	35.9	104	59.4	141	50.7
Patients with peripheral neuropathy in 1999 but free from it in 2004	-	-	1	0.6	1	0.3
Total	103	100	175	100	278	100

^aP<0.05; ^bP<0.01

Figure 1. Prevalence of peripheral neuropathy at two time points five years apart.



symptoms and signs in 1999, but did show them in 2004. The rate of polyneuropathy development was significant for type 1 diabetes at a level of $P<0.01$.

In type 2 diabetics, the symptomatology of polyneuropathy was significantly more pronounced at both time points. The difference reached a higher level of statistical significance in female patients.

The prevalence of polyneuropathy reported from various studies differs, ranging from 20% to 50%. Duration of diabetes exerts the main impact on the results (6). Our results obtained at both time points revealed a significantly higher prevalence of diabetic polyneuropathy for both types of diabetes in both sexes, and direct dependence on the duration of diabetes, which was statistically more significant in females (Fig.1). It should also be noted that the mean

diabetes duration in our sample was 13.07 ± 6.81 years. Our results correspond to the results of Boulton *et al.* (1991) who report on the overall prevalence of distal symmetric multiple neuropathy in type 1 and 2 diabetics based on clinical criteria to range from 25% to 30%, increasing to 40% and higher in older diabetics (7). Thomas (1999) suggests that in typical population of type 1 and 2 diabetics in Europe and North America the prevalence of peripheral diabetic neuropathy reaches 50% after 20 years of diabetes duration. Our results correspond to those reported by Thomas (8). According to Thomas *et al.* (1991), one third of all diabetics suffer from significant peripheral neuropathy, but there are also signs and symptoms of polyneuropathy in 17% of newly discovered diabetics (9). Walter *et al.* (1992) suggest that peripheral motor sensory neuropathy, the primary cause or contributing factor in most cases of foot ulcerations, becomes more frequent with age and affects 25% of type 2 diabetics aged 80+ years (10). According to the International

Working Group on the Diabetic Foot (1999), an estimated prevalence of peripheral neuropathy varies between 30% and 70%, depending on the tested population, definition and diagnostic criteria (11).

CONCLUSION

In conclusion, diabetic neuropathy was significantly more common in 2004 compared to 1999 in the same group of patients ($P < 0.01$). The longer the duration of diabetes, the higher is the risk of diabetic neuropathy development ($P < 0.05$). Diabetes duration is the key factor for the development of microvascular complications of neuropathy. In our study, the risk was greater in female patients with type 2 diabetes. Accordingly, a more aggressive approach is needed in the treatment of diabetics in our setting. It should include education, dietary advice, physical activity and appropriate use of medication.

REFERENCES

1. Boulton AJM, Malik RA. Diabetic neuropathy. *Med Clin North Am* 1998;82:909-929.
2. Harati Y. Diabetes and the nervous system. *Endocrinol Metab Clin North Am* 1996;25:325-359.
3. Pickup JC, Williams G. Textbook of diabetes, 3rd ed. London (UK): Blackwell Science Ltd., 2003.
4. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005;28:956-962.
5. Jurado J, Bataller F, Dorca A, Garcia F, Brossa N, Barnera T, et al. Diabetic foot risk factors in diabetic patients with and without polyneuropathy. The North Catalonia Diabetes Study. *Diabetologia* 2004;47(Suppl 1):A373. I-VIII Proceedings of the 40th EASD Annual Meeting of the European Association for the Study of Diabetes; Munich, Germany.
6. Aaberg ML, Burch DM, Hud ZR, Zacharias MP. Gender differences in the onset of diabetic neuropathy. *J Diabetes Complications* 2008;22:83-87.
7. Boulton AJM, McLeod AF, Williams DRR, Sonksen PH. The prevalence of diabetic neuropathy in patients attending UK hospital clinics. *Diabetologia* 1991;34(Suppl.2)A:36.
8. Thomas FJ. Diabetic peripheral neuropathies: their cost to patient and society and the value of knowledge of risk factors for development of interventions. *Eur Neurol* 1999;41:35-43.
9. Thomas FJ, Veves A, Ashe H, Knowles EA, Gem J, Walker MG, et al. A team approach to diabetic foot care: the Manchester experience. *Foot* 1991;1:75-82.

10. Walters DP, Gatling W, Mullee MA, Hill RD. The prevalence of diabetic distal sensory neuropathy in an English community. *Diabet Med* 1992;9:349-353.
11. International Working Group on the Diabetic Foot. *International Consensus on Diabetic Foot*. Amsterdam, The Netherlands; 1999.