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COGNITIVE DYSFUNCTIONS IN DIABETIC POLYNEUROPATHY.

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SUMMARY:

Introduction: The objective of our study was to examine cognitive status, short – term memory, delayed recall and the retention of visual information in diabetics with polyneuropathy and to establish the impacts of some risk factors on cognitive performance.

Contingent and methods: We assessed 47 diabetic patients with polyneuropathy, using the Mini Mental State Examination, 10 words test, the Benton visual retention test and the Hamilton scale.

Results: Global cognitive dysfunction, decline in verbal memory and visual retention and tendency for depressive mood were observed. We found statistically significant interaction of ageing, sex, severity of pain, duration and late onset of diabetes mellitus (DM) on cognitive functioning. Therapy association on cognition was not found.

Conclusions: Our study confirms the hypothesis of global cognitive dysfunction, associated with diabetic polyneuropathy. The interactions of sex and pain severity require further study. We arise a hypothesis of asymmetrical brain injury in diabetics.

Key words: diabetic polyneuropathy, global cognitive functioning, retention of visual information, verbal memory

INTRODUCTION:

Diabetes mellitus is a well known complex chronic metabolic disorder[1]. A growing number of studies have shown that diabetes is associated with impaired cognitive processes[2, 3]. In cases with questionable dementia, DM is associated with a faster rate of cognitive decline (measured by Mini-Mental State Examination)[3], while such an association is questionable in individuals without dementia[3, 4, 5]. The risk of depression in diabetics[6, 7] is two times higher than in controls furthermore the depression itself could lead to mild cognitive decline. Some studies on diabetics have indicated decline in certain cognitive domains[8] such as verbal memory, attention and executive functions, as well as visual retention/visual working memory[5] (despite of some negative results[9]).

The following factors have been pointed as risk factors for cognitive decline in diabetes mellitus: early onset of DM[10] (before the age of 65), male sex[11] (although more recent studies have denied such association[3, 12]), aging[13], complications of DM[12, 14], insulin therapy[15, 16], duration and severity of DM[16], and others (such as education, profession, depressive mood, history of transient ischemic attacks, hyper and hypoglycemic episodes during testing).

The objective of our study was to examine cognitive status, short – term memory, delayed recall and the retention of visual information in diabetics with polyneuropathy and to establish the impacts of some risk factors on cognitive performance.

CONTINGENT AND METHODS:

Contingent: We studied 47 patients with diabetic polyneuropathy (males 38.3%, females 61.7%; age: average 60.85, Median 61.0; Mode 60; SD 10.8511) in the Department of Neurology and Neurosurgery – Medical University Pleven. They were considered eligible for the study if they met the following criteria: 1. Diabetes mellitus (DM), diagnosed by endocrinologist through the American Diabetes Association Criteria. 2. EMG finding for polyneuropathy. 3. Formal education (minimum 8 years). The exclusion criteria were: lack of interest, refusal, and other neurologic diseases, moderate or severe systemic and psychiatric diseases (except depression). Written informed consent was obtained from all the participants.

Methods: In this cross – sectional study, patients underwent an assessment which included clinical evaluation by neurologist and endocrinologist, EMG investigation, blood and urine samples examinations. For our purposes we used the following neuropsychological battery: Mini – Mental State Examination (MMSE), Test of 10 words for short term memory and delayed recall, Benton visual retention test Administration A, Form E (BVRT), 21 Hamilton scale (HS). The severity of pain was assessed with Visual Analogue Scale (VAS). Information about the concomitant medication was taken from the official medical records ("recepturna knizka"). The patients were divided into groups according sex, type of therapy (25.53% on insulin, 65.96% on tablets, 8.51% - insulin plus tablets) and onset of DM (85% early – before the age of 65 and 15% late – after the age of 65).

Statistical analysis: STATGRAPHICS 5.0 Plus free version was used. One-way and multifactor ANOVA and simple and multiple regression analyses were applied. All statistical tests were interpreted at 5% significance level.

RESULTS:

The basic statistical results are shown in Table 1. Cognitive decline was found in 51% of our patients, short – term memory impairment in 79% and hypomnesia for delayed recall in 81% (figure 1, 2 and 3). The influence of examined risk factors on MMSE score are given in Table 2. Early onset of DM was associated with better cognition than the later one, after removal of the aging factor (p=0.0035, Kruskal – Wallis p = 0.0189837). Interactions of the examined risk factors on short-term memory and delayed recall respectively are given in Tables 3 and 4. The early onset of DM was associated with more significant decline in delayed recall abilities, independently from aging factor (P=0.0336, Kruskal – Wallis p = 0.0404). The relationships between examined risk factors and BVRT are shown in Tables 5, 6, 7 and 8. Statistically males had more correct answers than women. The early onset of DM (after aging factor removal) was associated with more correct answers and less errors on BVRT. Patients had a total of errors in which the errors on the left side were predominant compared to the errors on the right side (Kolmogorov – Smirnov Test p=0.0004). The number of errors in left visual field increased with the duration of DM (ð=0.0494), but such association was not found for the number of errors in the left visual field (p≥0.05). We discovered a strong relationship between VAS and HS scoring (F=219.87, P= 0.0001, CC= 0.9111). The results of interactions of risk factors on subtypes of BVRT errors are summarized in Table 9.

Fig. 1. Cognitive status

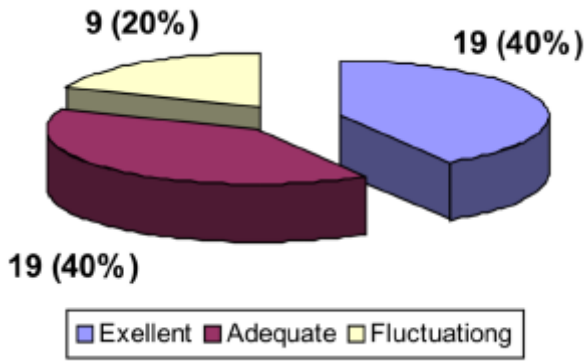

Fig. 2. Cognitive status

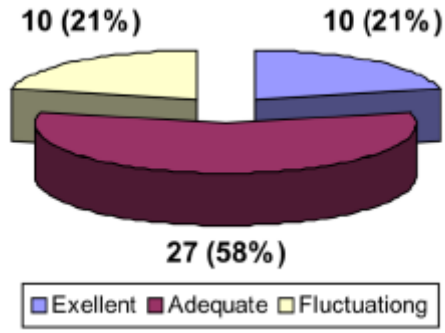

Fig. 3. Cognitive status

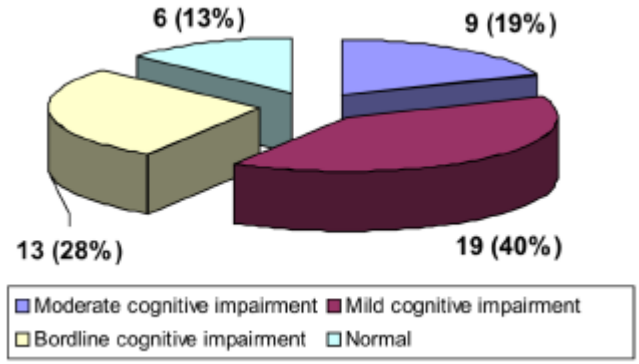

Table 1. Main statistical data

	Average	Median	Mode	Standard deviation	Interval
MMSE	22.9362	24	26	3.99132	11 to 28
Short time verbal memory	6.04255	6.4		1.15189	3.2 to 7.8
Delayed recall	5.3829	6.0	6.0	1.68824	0 to 9
BVRT correct answers	3.31915	3.0		1.9683	0 to 7
BVRT total errors	11.2979	11.0	8.0	5.08157	4 to 21
BVRT errors in left visual field	6.48936	6.0		3.26957	1 to 12
BVRT errors in right visual field	4.34043	4.0	4.0	1.94798	1 to 8
VAS	6.94681	7.0	7.0	1.48994	4 to 9
HS scoring	16.1064	16.0		6.80228	6 to 29

Table 2. Influence of aging, sex, duration of DM, treatment, DM onset, Hamilton scoring and pain severity on MMSE results

	AGING	SEX	Duration	Treatment	Onset	Hamilton	VAS
F =	10.92		9.78			23.23	25.09
P =	0.0019	p≥0.05	0.0031	p≥0.05	p≥0.05	0.0001	0.0001
CC =	-0.44187		-0.42261			-0.583457	-0.59827

Table 3. Influence of aging, sex, duration of DM, treatment, DM onset, Hamilton scoring and pain severity on short – term memory

	AGING	SEX	Duration	Treatment	Onset	Onset before/ after 65	Hamilton	VAS
F=	5.60		9.54				16.29	21.08
P=	0.0223	p≥0.05	0.0034	p≥0.05	p≥0.05	p≥0.05	0.0002	0.0001
CC	-0.3327		-0.4181				- 0.5155	-0. 5649

Table 4. Influence of aging, sex, duration of DM, treatment, DM onset, Hamilton scoring and pain severity on delayed recall

	AGING	SEX	Duration	Treatment	Onset	Hamilton	VAS
F=	7.54		5.57			10.29	12.86
P=	0.0086	P≥0.05	0.0226	P≥0.05	P≥0.05	0.0025	0.0008
CC=	- 0.3789		- 0.3320			-0.4314	-0.4714

Table 5: Influence of aging, sex, duration of DM, treatment, DM onset, Hamilton scoring and pain severity on number of correct answers on BVRT.

	AGE	SEX	Duration	Treatment	Onset	Onset before/after 65	Hamilton	VAS
F=	14.79	4.38	4.19		5.58	4.93	15.48	20.29
P=	0.0004	0.0419	0.0466	P≥0.05	0.0225	0.0316	0.0003	0.0001
CC=	0.4974		- 0.2917		- 0.3322	KW p=0.0243	-0.5059	-0.5575

Table 6: Influence of aging, sex, duration of DM, treatment, DM onset, Hamilton scoring and pain severity on number of total errors on BVRT

	AGE	SEX	Duration	Treat-ment	Onset	Onset before/after 65	Hamilton	VAS
F=	15.53		5.85		4.57		11.11	16.71
P=	0.0003	P>0.05	0.0197	P>0.05	0.0346	0.0085	0.0017	0.0002
CC	0.5065		0.3391		0.3089	KW p=0.0172	0.4450	0.5204

Table 7: Influence of aging, sex, duration of DM, treatment, DM onset, Hamilton scoring and pain severity on number of total errors in left visual field

	AGE	SEX	Duration	Treatment	Onset	Onset before/after 65	Hamilton	VAS
F=	10.96		4.08			4.66	5.53	9.54
P=	0.0018	P>0.05	0.0494	P>0.05	P>0.05	0.0363	0.0231	0.0034
CC=	0.4426		0.2882			KW p=0.0378	0.3309	0.4182

Table 8: Influence of aging, sex, duration of DM, treatment, DM onset, Hamilton scoring and pain severity on number of total errors in right visual field

	AGE	SEX	Duration	Treatment	Onset	Onset before/after 65	Hamilton	VAS
F=	12.29				4.87	9.77	12.51	17.64
P=	0.0010	P>0.05	P>0.05	P>0.05	0.0324	0.0031	0.0010	0.0001
CC=	0.4631				0.3126	KW p=0.0092	0.4664	0.5306

Table 9. Relationships between aging, sex, MMSE, short – term memory, delayed recall, Hamilton scoring, VAS, scoring, duration, treatment and onset of DM and subtypes of errors on BVRT

		Omissions	Distortions	Perseverations	Rotations	Misplacements	Size errors
Ageing	F=	6.92					
	P=	0.0116	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
	CC=	0.3651					
Sex	P=	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
MMSE	F=	10.63	13.32	6.40		4.75	
	P=	0.0021	0.0007	0.0150	p>0.05	0.0345	p>0.05
	CC=	-0.4371	-0.4779	-0.3529		-0.3091	
Short - term memory	F=	21.03		7.60		4.43	
	P=	0.0001	p>0.05	0.0084	p>0.05	0.0410	p>0.05
	CC=	-0.5644		-0.3801		-0.2993	
Delayed recall	F=	19.27		8.17		6.82	
	P=	0.0001	p>0.05	0.0064	p>0.05	0.0122	p>0.05
	CC=	-0.5475		-0.3919		-0.3628	
Hamilton	F=	4.95					
	P=	0.0311	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
	CC=	0.3149					
VAS	F=	4.70	5.89				
	P=	0.0355	0.0193	p>0.05	p>0.05	p>0.05	p>0.05
	CC=	0.3076	0.3402				
Duration	P=	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Treatment	P=	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Onset	P=	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05

DISCUSSION:

Our study confirms that diabetics with polyneuropathy have an increased risk for global cognitive decline, impairment of verbal short-term memory, delayed recall and visual retention of information, as well as increased tendency for depressive mood (HS scoring average 16.1064, SD 6.80228) compared to whole population data. The latter was strongly associated with pain severity (F=219.87, P= 0.0001, CC= 0.9111). We found left/right visual retention asymmetry, which might be related to the asymmetrical brain injury. It seemed that right hemisphere was more vulnerable to diabetes-related complications. As we expected, aging and depression were associated with decline in all examined cognitive domains. To our knowledge, there are no other studies on the relationship between pain severity in diabetic polyneuropathy and cognitive functioning. We discovered a statistically significant relationship between pain severity and cognitive decline. Pain severity should be treated as an independent risk factor for cognitive decline and depression in diabetic polyneuropathy adults. According to recent studies no association was found between gender and cognition, except for the number of correct answers on BVRT (men have statistically more correct answers than women). It has been hypothesized that diabetes is a potential risk factor for cognitive decline predominantly in women compared to men, due to a higher risk of diabetes in females, related to microvascular disease and early loss of possible protective effects of estrogen on cognitive functioning[17]. Another possible explanation of that finding is that males have better abilities to remember and draw figures than women, due to their better logistical memory capacity. We did not find any association between the type of therapy and cognition, which is a controversial to the findings from previous studies[15,16]. Despite the representativeness of our study of participants of the target population, the possibility for statistical bias could not be completely ruled out, moreover our type of therapy samples were relatively small, which could explain our conclusions. With increasing of DM duration all examined cognitive functions declined, however left/right visual retention duration asymmetric decline was found, which gave us the basis to raise the hypothesis of asymmetrical injury of brain hemispheres in diabetics. Although the opposite previous studies' results[16], after additional control for aging, late onset of DM was associated with poor visual retention of information than earlier. Onset of DM before 65 was associated with better visual retention (after aging factor removal), a fact that needs to be proved by future studies.

Interesting conclusions were observed from the analysis of subtypes BVRT errors. The number of omissions increased with decline of global cognitive performance and verbal memory and with increasing of pain and depression severity. It seemed that omissions were strongly dependant on individual cognitive functions and emotional state and that they had the greatest variability among subtypes of BVRT errors. The number of distortions was only related to global cognition and severity of pain. As we expected, the number of perseverations increased only with decline in global cognition and verbal memory supposedly due to frontal lobe dysfunction, no relationship was found with Hamilton or VAS scoring. The number of misplacements increased with global functioning decline and was in relationship with verbal memory. The numbers of rotations and size errors were in no association with other examined cognitive domains. Lack of statistically significant association between numbers of subtypes BVRT errors and duration, treatment and the age of onset of DM was established. So we observed significant relationship between declines of visual and verbal memory in diabetic adults.

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