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ORIGINAL ARTICLE

Spinal cord lesions in diabetes mellitus. Somatosensory and motor evoked potentials and spinal conduction time in diabetes mellitus

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Abstract

OBJECTIVES: Diabetic neuropathy and autonomic nervous system neuropathy are recognized as the most common clinical pictures of nervous system disorders caused by diabetes mellitus (DM). Damage to the brain and the spinal cord is rare. The aim of this work is to show the importance of somatosensory and motor evoked potentials (SEP and MEP) for the early diagnosis of nervous system damage related to diabetes mellitus.

MATERIAL AND METHODS: We examined spinal and cortical somatosensory evoked potentials (SEP) after median and fibular nerve stimulation in diabetics and control subjects. We measured the latencies of individual wave deflections and peripheral and central conduction time (PCT and CCT) of spinal and cortical SEP. Similarly, transcranial magnetic stimulation was used for measuring the central and peripheral conduction time (CCT and PCT) in a group of type 1 diabetics and a control group of volunteers.

RESULTS: The examination SEP and MEP proved and confirmed the prolongation not only of peripheral conduction time, but also of the central conduction time – especially in spinal cord structures. An assumption that spinal cord changes are connected with the decreased number of myelinated fibers able to conduct the impulses from periphery and brain cortex, respectively, has to be accepted.

CONCLUSIONS: The results suggest that the use of somatosensory and motor evoked potentials (SEP and MEP) examination and conduction times measurement has significance in the confirmation of unapparent lesions of the spinal cord in diabetics of both types.

Introduction

Diabetes mellitus (DM) is the result of absolute or relative hypoinsulinemia, and is currently described as an endocrine disease that causes damage to many organs and systems. Vulnerability and long-term complications are typical for patients with all types of DM. The most important factors in the pathogenesis of multi-system damage in DM are metabolic and vascular changes directly caused by hyperglycemia.

The nervous system (NS) belongs to the organ systems that are often impaired by DM, with symptoms usually developing 15 to 20 years following the appearance of hyperglycemia. While the damage of the NS is rarely a direct cause of death, it is very frequently a major cause of morbidity.

Diabetic neuropathy and autonomic nervous system neuropathy are recognized as the most common clinical pictures of nervous system disorders caused by DM, while the damage of the brain and the spinal cord [1,12] are considered to be rare. In the diagnosis of nervous system damage, noninvasive methods such as biochemical and electrophysiological tests are used and preferred. The early recognition of the damage is clinically and therapeutically important because patients examined often do not express apparent signs of NS disorder.

Electrophysiological diagnostic methods in the diagnosis of diabetic neuropathy, namely the electromyography (EMG) and nerve conduction studies, are used. The importance of these methods has to be stressed, with respect to the dominance of sensitive and motor function impairment in a diabetic patient.

The aim of this work is to indicate the importance of somatosensory and motor evoked potentials (SEP and MEP) for the early diagnosis of nerve system damage related to diabetes mellitus.

Material and methods

We studied 20 patients (aged 35–50 years) with type 2 diabetes mellitus, each presenting with the disease for 5–10 years. Each patient gave his or her informed consent for inclusion in the study. The disease was compensated either by diet or by oral antidiabetic agents. No clinically detectable nervous system disorders were present in this group of patients. The control group population comprised of 30 healthy individuals of the same median age.

The spinal and cortical SEPs after median and fibular nerve stimulation were examined in both groups of patients. We measured the latencies of individual wave deflections, and peripheral and central conduction time (PCT and CCT) of spinal and cortical SEP. The somatosensory evoked potentials were measured after the rectangular impulse stimulation of both nerves (median and fibular). The impulses were generated by a Medelec MS-92 apparatus, with stimulus intensity greater than 20 mA, duration of 0.1 ms, and pulse frequency of 5 Hz, according to the method described by Buranova et al. in 1985 [3]. The analysis times were 100 ms and 50 ms in spinal SEP, respectively. In the median nerve the stimulation electrode was placed in the wrist region and the registration electrodes were placed in the region of the fifth cervical vertebra and on electrode position C3, C4 according to the 10–20 international electroencephalographic electrode placement system. The reference electrode was placed on the earlobe. The measurements were undertaken at least two times in all patients. The conduction velocity of sensitive nerve fibers was measured continually.

The identification of the wave deflection was according to the following: P9 – volley from brachial plexus, N14 – impulse entry into the nuclei of posterior column, P15 – thalamic wave deflection and N20 is the first cortical response.

The SEPs after fibular nerve stimulation were recorded with the stimulation electrode placed in the region of capitulum fibulae. The registration electrodes in spinal SEPs were placed on the processus spinosus of Th12 vertebra, the reference electrode was placed on crista iliaca anterior. The registration electrode in cortical SEP was placed on the electrode position C2 according to the 10–20 international system and the reference electrode was placed on the left earlobe.

The identification of the wave deflection was according the following: N17 – volley from the sciatic nerve, N21 is impulse entry into the spinal cord horns, P35 is a thalamic wave deflection, and N40 is the first cortical response.

We also measured the peripheral (PCT) and central (CCT) conduction times after the stimulation of both median and fibular nerves. The peripheral conduction time was defined as the time interval between time of nerve stimulation and time of wave deflection generated by either median nerve [from the nuclei of posterior columns (N14)] or fibular nerve [from spinal cord horns (N21)].

In cortical SEP (CSEP), the N20 and N40 wave deflections were the most important. These deflections limit the duration of CCT. For evaluation of hemispheric conduction velocity, P15 and P35 wave deflections generated in thalamic nuclear structures are the most important. These deflections have the highest importance in our aim to separate the CCT in relation to spinal and cerebral pathway conduction times (sCCT and cCCT).

If the value of CCT after median nerve stimulation is normal, then the calculation of spinal CCT after fibular nerve stimulation is:

$$\mathbf{sCCT = P35 - N21}$$

if CCT after median nerve stimulation is abnormal (prolongation), then sCCT is:

$$\mathbf{sCCT = P35 - N21 - (P15 - N14)}$$

Statistical results were calculated by the Student's T test.

For CCT calculation using transcranial magnetic stimulation (TMS) we examined 148 patients [age 17–41 years, median 26.0, men 91 (61.5%), women 57 (38.5%)]. All patients had more than 10 years history of type I diabetes mellitus. Patients with positive symptoms or signs of focal CNS lesion were excluded. The control group comprised 27 healthy volunteers [aged 17–33 years, median 26.5, men 9 (33.3%), women 18 (66.7%)] with no history of neurological disease and no signs of focal CNS lesion.

Stimulation of supramaximal intensity of ulnar nerve at the wrist and peroneal nerve at the ankle was performed; F-wave and M-wave latencies were recorded using surface electrodes (Dantec) from the first dorsal interosseus muscle and extensor digitorum brevis muscle, respectively. The responses were recorded by EMG device Nicolet Viking IV P. Skin temperature did not drop below 32°C, room temperature was held within the range of 23–26°C.

Motor evoked potentials (MEP) were recorded from the above mentioned muscles. We used a magnetic stimulator MagPro Dantec. Only cortical stimulation was performed. A spiral magnetic coil with 14 cm diameter was positioned on the vertex (for upper extremity measurement) and Fz point of 10–20 international system (for lower extremity measurement), respectively. A single unrepeated stimulus was applied, 50–60% of maximum stimulator output and biphasic pulse magnetic field during mild muscle contraction (approx. 30% of maximal muscle strength) was used. We evaluated 2–5 responses; the inter-stimulus interval was more than 3 seconds. The latency was measured from the first visible deflection from the baseline. The shortest latency was evaluated. Filters were set in the range 1–10 kHz.

For CCT calculation we used a formula proposed by Rossini [10]:

$$\mathbf{CCT = MEP - [0.5 \times (F - M - 1) + M]},$$

where MEP is the latency of motor evoked potential, and F and M are latencies of F-wave and M-wave, respectively. The constant 1 reflects the one millisecond slowing needed for back-firing of upper motor neuron (the principle of F-wave formation).

Statistical evaluation of quantitative features was made by non-parametric variance analysis (Mann–Whitney U test) and parametric T test for independent variables with Welsch approximation for groups with unequal variances.

Results

Spinal SEP (SSEP) and cortical SEP (CSEP) responses were measured after median and fibular nerve stimulations. Time latencies and wave deflection amplitudes as well as CCT and PCT were evaluated separately (Table I, Table II).

In the assessment of spinal SEP we evaluated the N9 and N14 wave deflections after median nerve stimu-

Table I. The values of the latencies (ms) of spinal and cortical SEPs and peripheral and central conduction times after median nerve stimulation

SEP CV5/C3-C4	Control group (n=30) Latencies (ms) mean ± SD		DM 2nd type (n = 20) Latencies (ms) mean ± SD	
	Left	**Right**	**Left**	**Right**
N9	10,1 + 1,4	10,1 + 1,8	12,6 + 2.1 xx	12,6 + 3,0 x
N14	14,1 + 1,3	14,0 + 1,9	16,3 + 3,6 x	16,1 + 3,1 x
P15	16,5 + 4,1	16,8 + 4,2	17,0 + 3,6	17,6 + 3,9
N20	20,7 + 2,2	20,4 + 3,1	23,3 + 4,4 xx	23,0 + 4,8 x
PCT	14,1 + 1,3	14,0 + 1,9	16,3 + 3,6 x	16,1 + 3,1 x
CCT	6,6 + 1,4	6,4 + 1,6	7,0 + 1,8	6,9 + 1,4

x – p < 0,05 xx – p < 0,01

Table II. The values of the latencies (ms) of spinal and cortical somatosensory evoked potentials and peripheral and central conduction times after fibular nerve stimulation

SEP T12/Cz		Control (n = 30) Latencies (ms) mean ± SD		Diabetes mellitus 2nd type (n = 20) Latencies (ms) mean ± SD	
		Left	**Right**	**Left**	**Right**
	N17	17,1 + 2,3	17,1 + 2,7	19,1 + 2,6xx	20,0 + 1,9 xx
	N21	19,9 + 2,6	20,5 + 3,1	22,0 + 2,0 xx	23,4 + 1,6 xx
	P35	34,2 + 3,6	34,5 + 3,3	40,0 + 3,9 xx	40,4 + 2,6 xx
	N40	40,4 + 4,0	41,3 + 4,8	47,0 + 3,6 xx	47,4 + 4,5 xx
	PCT	19,9 + 2,6	20,5 + 3,1	22,0 + 2,0 xx	23,4 + 1,6 xx
	sCCT (spinal)	20,5 + 2,4	20,8 + 2,5	25,0 + 2,4 x	24,0 + 2,2 x
CCT	**cCCT (cerebral)**	6,2 + 1,2	6,8 + 1,5	7,0 + 1,6	8,0 + 1,9
	CCT (total)	26,7 + 1,9	27,6 + 2,0	32,0 + 1,9 x	32,0 + 2,0 x

x – p < 0,05 xx – p < 0,01

lation and N17 and N21 wave deflections after fibular nerve stimulation. These deflections represent the activity generated in brachial and lumbosacral plexi, in nuclei of posterior columns (wave deflection N14) and of posterior horns (wave deflection N21), thereby defining the PCT.

In evaluation of the wave deflections after median and fibular nerve stimulation more important changes were observed in SSEP and CSEP of the fibular nerve. After median nerve stimulation, significant changes in latencies were present in SSEP. The latencies of cortical SEP responses were slightly delayed.

On the contrary, after the fibular nerve stimulation latencies of both SSEP and CSEP responses were significantly (p<0.0l) prolonged. In CSEP the amplitude decrease of wave deflection was found.

The evaluation of PCT and CCT displayed some different characteristics in SSEP and CSEP after median and fibular nerve stimulations. The PCT and CCT prolongation was less significant than in the stimulated median nerve (p<0.05) than in the fibular nerve (p<0.0l).

The comparison of sCCT and cCCT conduction times showed that in a group of diabetic patients the spinal cord structures are responsible for the prolongation.

Result from TMS examination are summarized in the following tables (Table III–V).

Using MEP latency, motor response latency (M) and the shortest F-wave latency from right ulnar and left peroneal nerves, we calculated the central conduction time (CCT) [10] (Table V).

Statistical comparison of CCT values recorded in diabetic and control groups from UE (CCT_{UE}) showed no significant differences (p<0.70). Comparing the CCT values recorded from LE (CCT_{LE}) the statistical significance was significant (p<0.05).

Electrophysiological testing of peripheral impairment in diabetic patients showed signs of peripheral neuropathy in 87 (58.8%) patients.

Discussion

The opinion that a typical clinical picture of nervous system involvement in diabetes is a polyneuropathy accompanied in most of the cases with neuropathy of the autonomic nervous system, dominates in most contemporary works. It is also assumed that the damage of CNS – brain and the spinal cord – is very rare and most of these cases are caused by vascular changes in cerebral circulation. The vascular changes altogether with metabolic disturbance are considered to be the most important factor in development of the peripheral and central nervous system lesion. The blood-brain barrier damage is a main cause of the hyperproteinorhachia in 65% of DM cases (and heavy proteinorhachia with protein content in CSF reach more than 1000 mg/l in 15% of cases) also has been considered [2,7,12].

The diagnostic method commonly used in evaluation of the nervous system lesion is EMG combined with conduction studies of sensitive and motor nerves. We decided to use SEP and MEP measurements, which represents functional integrity of the sensitive and motor pathways of the nervous system. In this study we also used the CCT and PCT measurement [2,3,5]. The integrity of sensitive pathways is necessary for correct implementation of motional (movement) patterns [6,9,11,13,14,15]. The integrity of the motor system is inevitably required for the implementation of the special motor functions, and plays a very important role in motoric functions.

Table III: Control group (n = 27) – upper (UE) and lower (LE) extremity MEP latencies

Control group.	MEP_{UE} (ms)			MEP_{LE} (ms)		
N = 27	$\bar{x}$	SD	Median	$\bar{x}$	*SD*	*Median*
	21,5	1,72	21,3	37,8	2,9	37,9

Table IV: Patients with DM I (n = 148) - upper (UE) and lower (LE) extremity MEP latencies

DM I	MEP_{UE} (ms)			MEP_{LE} (ms)		
N = 148	$\bar{x}$	SD	Median	$\bar{x}$	*SD*	*Median*
	23,2	2,1	23,3	40.4	3.6	41,1

Table V: CCT values in the control and diabetic groups

	CCT_{UE} (ms)			CCT_{LE} (ms)		
	$\bar{x}$	SD	Median	$\bar{x}$	SD	Median
Control	6,73	1,06	6,85	12,28	1,67	12,15
DM I	6,93	1,39	7,03	13,04	2,49	12,85

The SEP and MEP changes are also connected with aging, as a result of the decrease in the number of myelinated fibers of the nerve roots and spinal cord, and as a result of degenerative changes in posterior columns and in the pyramidal tracts [4,6,8]. These assumptions are in concordance with current information on morphologic changes in spinal cord fibers and pathways and our findings about changes of CCT and PCT of the spinal cord in diabetic patients.

Transcranial magnetic stimulation could be the method of choice in diagnostic procedures of early changes of CNS damage in DM. Results of our study show statistically significant slowing of conduction time along the central motor pathways in the longest part of pyramidal tract connecting the motor cortex with α-motorneurons in the lumbar intumescence. Because the important prolongation of CCT was present only in pyramidal tract lesions for lower extremities, we assume damage predominantly of lower extremity motor tracts in comparison with upper extremity, and this fact indicates that the lesion of pyramidal tracts is localized above all (mainly) in the spinal cord. This phenomenon could be dependent on the length of axons, which evokes comparison to length-dependent injury in distal symmetrical diabetic neuropathy initially and mainly affecting the longest fibers. We propose that a "central length-dependent injury" resulting in diffuse central-peripheral axonopathy could be responsible for predominant lesions of longer motor pathways in the spinal cord of diabetic patients too.

The above-mentioned morphological changes probably cause more important changes of conduction times after fibular nerve stimulation, and are probably connected with an erect posture and locomotion activity. The exclusion of thalamocortical hemispheric sensitive pathway (cCCT) makes it possible to prove (indirectly) the major share of spinal cord pathways on elongation of CCT in diabetes mellitus patients. We thus disclaim the rarity of spinal cord pathways impairment in diabetic patients. The axoplasmatic flow slowing is the cause of segmental demyelination of peripheral nerves and fibers. Especially the lesion of the spinal cord cause the deficiency of myelinated fibers even in diabetic patients with clinically unapparent damage with the disturbance of neural transmission.

Conclusion

We disclaim the rarity of spinal cord pathways impairment in diabetic patients and confirm that the use of SEP and MEP examination and conduction times measurement utilizing those techniques may play an important role in the confirmation of unapparent lesions of the spinal cord in diabetics.

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