CLINICAL STUDY

Clinically unapparent central motor pathways lesion in patients with type I diabetes mellitus
A transcranial magnetic stimulation study

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Abstract

Objective: **There is an evidence of central nervous system (CNS) involvement in diabetic patients. The aim of the study was to determine a conduction slowing in CNS pathways using a transcranial magnetic stimulation (TMS) and F-wave latency measurement.**
Methods: **Diabetic patients and a control group, both without clinical symptoms and signs of CNS lesion were evaluated. Motor evoked potentials were recorded from upper and lower extremities and central conduction time (CCT) was calculated according to formula: CCT=MEP–[0.5x(F-M-1)+M]. Obtained results and data from literature were compared.**
Results: **There was a significant prolongation of CCT recorded from lower extremities. The prolongation of CCT recorded from upper extremities was not statistically significant. Our results correlate with previously published data.**
Conclusion: **In spite of missing clinical signs of CNS lesion in diabetic patients, a significant prolongation of CCT compared to control group and literature data was recorded. We assume a presence of diffuse subclinical CNS lesion induced by metabolic changes in DM. Difference between CCT obtained from upper and lower extremities implicate, that changes are analogical to peripheral neuropathies ("central length-dependent injury?"). Measurement of CCT using TMS could become a complementary electrophysiological method for assessment of subclinical CNS involvement in diabetic patients.** ***(Tab. 4, Ref. 17.)***
Key words: transcranial magnetic stimulation, central conduction time.

Diabetes mellitus (DM) is a complex metabolic disorder, affecting metabolism of carbohydrates as well as lipids and proteins, caused by the lack of insulin. In type I diabetes, insulin is functionally absent due to autoimmune destruction of pancreatic beta cells. It is present most often in juveniles, starting in children aged 4 years and older, with the peak incidence at 11–13 years of age (1).

Diabetic neuropathy is the most common complication of DM, both in types 1 and 2. Individuals with type 1 DM usually develop neuropathy after more than 10 years. Concerning diabetic complications, neuropathy is associated with the highest morbidity and decreases the patient's quality of life (QOL). Factors involved in the pathogenesis of diabetic neuropathy include metabolism, vascular insufficiency, loss of growth factors, and autoimmune destruction of small unmyelinated nerves (C fibers) in visceral and dermal area. Hyperglycemia causes several biological changes, including an increased production of the advanced glycation end products, a defect in the polyol pathway, affection of the aldol reductase enzyme, and impaired resistance to oxidative stress. Nonspecific glycosylation of the axon and microvessel proteins may cause a decreased endoneural blood flow and resulting nerve ischemia, leading to both nerve and ganglia hypoxia and oxidative stress.

The two main features explaining symptoms and complications of diabetic neuropathy are though to be degeneration of nerve fibers and impaired blood vessels supplying them. Appropriate

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Tab. 1. Group characteristics of patients with type I DM.

Group	n	Sex		Age (years)		Duration of DM (years)
DM type I	148	M	F	x	min-max	≥10
		91	57	27.0±5.47	17–41	

Tab. 2. Control group (n=27) – MEP latencies of the upper (UE) and lower (LE) extremity.

Control group	MEP_{UE} (ms)			MEP_{LE} (ms)		
	x	SD	median	x	SD	median
n=27	21.5	1.72	21.3	37.8	2.9	37.9

Tab. 3. Patients with type DM I (n=148) – MEP latencies of the upper (UE) and lower (LE) extremity.

DM I	MEP_{UE} (ms)			MEP_{LE} (ms)		
	x	SD	median	x	SD	median
n=148	23.2	2.1	23.3	40.4	3.6	41.1

circulation determines whether nerve fibers repair themselves or proceed to total degeneration. Recent studies suggested that the loss of neurotrophic support contributes to the pathogenesis (2).

Whether the nerve axon or the Schwann's cell is damaged first, remains controversial. Microscopic nerve examination in diabetic patients without neuropathy has shown demyelination without axonal injury and may indicate that demyelination and affection of the Schwann's cell occur first (3).

The central nervous system (CNS) is usually not thought to be a target of chronic diabetic complications. Nonetheless, substantial evidence suggests that diabetes leads to the CNS damage. The pathophysiology of CNS abnormalities is uncertain; many conditions are probably involved in neural damage including chronic hyperglycemia, hypoglycemic episodes, angiopathy, blood-brain barrier dysfunction and others, still unknown. Several different techniques have been used to evaluate CNS damage induced by DM including histological examination (4, 5), measurement of spinal cord diameter using MRI (6), somatosensory evoked potentials in rats (7) and in humans (8, 9) and TMS using calculation of CCT from spinal and cortical MEP measurements (10, 11, 12).

In the study, a transcranial magnetic stimulation (TMS) in a consistent group of type I diabetic patients with different approach to CCT calculation (F-wave latency in contrary to a subtraction of spinal MEP from cortical one) is presented. TMS could be used as an elegant method for the evaluation of CNS changes even before the manifestation of clinical symptoms.

Material and methods

Patients

A group of 148 patients, aged 17–41 years (mean age 26.0), from the Diabetic outpatient department managed by Ľ. Barák, MD, PhD was examined. There were 91 men (61.5 %) and 57 women (38.5 %) in the group. All patients had more than 10-year history of type I diabetes mellitus. They were examined for the symptoms and signs of focal CNS lesion, patients with present symptoms or signs were excluded from the study (data are summarized in Table 1).

A group of 27 healthy volunteers aged 17–33 years (mean age 26.5) represents a control group. All control subjects had no history of neurological disease and displayed no signs of focal CNS lesion.

Methods

On the right upper extremity the F-wave and M-wave latencies were recorded, using surface electrodes (Dantec) placed on the first dorsal interosseous muscle, by supramaximal stimulation of the ulnar nerve at the wrist. On the left lower extremity were the F-wave and M-wave latencies recorded by surface electrodes placed on the short extensor digitorum muscle using a supramaximal stimulation peroneal nerve at the ankle. 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 above mentioned muscles. Using a magnetic stimulator MagPro Dantec, only cortical stimulation was performed. We used a spiral magnetic coil, 14 cm in diameter, positioned on the vertex (for upper extremity measurement) and Fz point of the 10–20 EEG standardization (for lower extremity measurement), respectively. A single unrepeated stimulus was applied, 50–60 % of maximal stimulator output, and a biphasic pulse magnetic field during mild muscle contraction (approx. 30 % of maximal muscle strength) were used. We evaluated 2–5 responses; 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 Kimura (13):

CCT=MEP–[0.5x(F-M-1)+M], where MEP is the latency of motor evoked potential, F and M are the latencies of F-wave and M-wave, respectively. The invariable 1 reflects about one millisecond slowing, needed for back-firing of upper motor neuron (the principle of F-wave formation).

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

Results

In the diabetic group (n=148) we were not able to record MEP in 4 subjects (0.02 %) and solely from lower extremities (LE), most likely due to severe peripheral neuropathy. In the control group we were able to record MEP from both lower and upper extremities (UE). The values of MEP latencies from both groups are summarized in Tables 2 and 3.

Tab. 4. CCT values in the control and diabetic group.

	DDT_{UE} (ms)			CCT_{LE} (ms)		
	x	SD	median	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

*p<0.70, **p<0.05

Using MEP latency, the motor response latency (M) and the shortest F-wave latency from right ulnar and left peroneal nerves, we calculated the central conduction time (CCT) according to the formula of Kimura (13) (Tab. 4).

CCT values of the diabetic group were statistically compared with CCT values of the control group and previously published data using the same technique (14).

We did not find a significant difference in CCT values obtained from lower and upper extremities between our control group and literature data. Statistical comparison of CCT values recorded in diabetic and control groups from UE (CCT_{UE}) showed no significant difference ($p<0.70$). When comparing the CCT values recorded from LE (CCT_{LE}), the statistical significance was significant ($p<0.05$).

Discussion

Nervous system complications of DM are not rare. In literature, the total prevalence is 47 %. Peripheral neuropathy is present in 97 % of cases while focal CNS lesion (ischemia, hemorrhage) in 5.5 % of cases (15). We could assume that DM causes, besides focal CNS lesion, also a diffuse CNS impairment. This kind of evidence is rare in literature and it is based on the impairment of cognitive abilities, radiological finding of brain and spinal cord atrophy or on the results of electrophysiological studies – visual, brainstem and somatosensory evoked potentials (16). It is assumed that diffuse changes in PNS and CNS are interrelated. The evolution of diffuse CNS changes in DM is gradual and insidious with relatively long clinically silent phase similar to peripheral neuropathy.

Transcranial magnetic stimulation could be the method of choice in the diagnostics of early CNS changes in DM. Our results showed a statistically significant slowing of nerve conduction along the central motor pathways in the longest part of pyramidal tract, ranging from motor cortex to α-motoneurons in the lumbal intumescence. Our results correlate with those previously published (10, 11, 12).

A very interesting finding of predominantly lower extremity motor tracts damage could depend on the length of axons which evokes analogy to length-dependent injury in distal symmetrical diabetic neuropathy, initially affecting the longest fibers. We propose that a "central length-dependent injury", resulting in diffuse central-peripheral axonopathy, could be responsible for predominantly longer motor pathways lesion in diabetes.

Calculation of the central conduction time (CCT) using F--wave reflects only pyramidal tract conduction while subtraction of the spinal latency from cortical latency comprises the conduction of axonal segment of the upper motor neuron, from vertebral body to intervertebral foramen (17). That is why we prefer this more precise method, though more time-spending, for CCT calculation. We did not find a significant difference in CCT normative data between our control group and literature data what proves reproducibility of the chosen method.

In spite of missing clinical signs of central motor pathways lesion in our diabetic patients we recorded a significant prolongation of central conduction time from lower extremities, compared to control group and previuously published data. As we did not find signs of focal CNS lesion we can assume, a presence of diffuse central motor pathways lesion caused by metabolic changes in DM. Difference between CCT obtained from upper and lower extremities (significant prolongation recorded only from lower extremities) could implicate changes analogical to peripheral neuropathies ("central length-dependent injury").

Measurement of central conduction time using TMS could become a complementary electrophysiological method for the assessment of the central motor pathways involvement in diabetic patients.

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NEW BOOK

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