Early Involvement of Central Nervous System in Type I Diabetic Patients

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OBJECTIVE — To investigate whether the asymptomatic involvement of the central and peripheral nervous systems may be an early complication of diabetes.

RESEARCH DESIGN AND METHODS — We studied early impairment of the central and peripheral nervous system pathways in 15 type I diabetic patients with good metabolic control and short disease duration and in 10 healthy control subjects using a set of neurophysiological tests.

RESULTS — Results in diabetic subjects showed *1*) impairment of motor (7%) and somatosensory (13%) pathways of the central nervous system, 2) impairment of motor and sensory conduction velocities (40–60%), and 3) normal values of the vibration perception threshold and cardiovascular autonomic tests.

CONCLUSIONS — The damage is more evident in peripheral sites where hyperglycemia and aldose reductase pathways are more active. Instead, several episodes of hypoglycemia, which occur in type I diabetic patients in good metabolic control, may cause alterations of brain nervous cells.

The impairment of the central nervous system (CNS) is a problem common in diabetes; the alteration of metabolic control with hyper- and hypoglycemia results in modifications of brain transport, blood flow, and metabolism and can provoke histological damage with selective neuronal necrosis (1). The continuous evolution of neurophysiological techniques helps to detect even latent alterations, including those of the CNS. Several studies have evaluated the early impairment of the CNS in diabetic patients by means of somatosensory-evoked potentials (SEPs) (2–3), but currently no studies have been conducted with patients having short duration of diabetes and good metabolic control. Furthermore, little is known about central motor pathways in diabetic patients using single-pulse high-voltage stimulation of the motor cortex and cervical spine segment. The percutaneous magnetic stimulation of central motor pathways (4–5) is a major advance in the study of conduction in central motor pathways. This technique is used in the study of fiber conduction in central motor pathways in a variety of neurological disorders, notably in multiple sclerosis (6); in a preliminary report (7), however, we used it for the first time to explain CNS alterations in type I diabetic patients.

RESEARCH DESIGN AND METHODS

We studied 15 type I diabetic patients (30 ± 3 years of age) with a duration of diabetes <5 years and near-normal metabolic control and 10 healthy control subjects matched for age and sex. The day before performing the neurophysiological tests, the metabolic profile was examined: fasting plasma glucose was 8.5 ± 0.6 mmol/l, HbA_{1c} 6.22 ± 1.3%, fructosamine 257 ± 28 μmol/l, and microalbuminuria 10.3 ± 3 μg/dl. Exclusion criteria were poor metabolic control, hypoglycemia (according to test on day 1), neurological diseases, symptoms of neuropathy, treatment with neurotrophic drugs, retinopathy, alcohol abuse, and kidney and liver diseases. The following parameters were studied: motor conduction velocity (MCV) of the peroneal nerve, sensory conduction velocity (SCV) of the sural nerve, SEPs after stimulation of the median nerve, *F* wave of the median nerve, motor-evoked potentials (MEPs) recorded from the abductor pollicis brevis (APB) after stimulation of the cortex and C7 (Erb's point), vibration perception threshold (VPT) at the great toe and ankle, and cardiovascular autonomic tests (CATs) (Valsalva ratio, lying-to-standing, standing-to-lying, deep breathing, and postural hypotension).

MCV and SCV were measured with a Medelec M6 instrument; VPT was evaluated with a Biothesiometer (Biomed-

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APB, abductor pollicis brevis; CAT, cardiovascular autonomic test; CNS, central nervous system; MCV, motor conduction velocity; MEP, motor-evoked potential; SCV, sensory conduction velocity; SEP, somatosensory-evoked potential; VPT, vibration perception threshold.

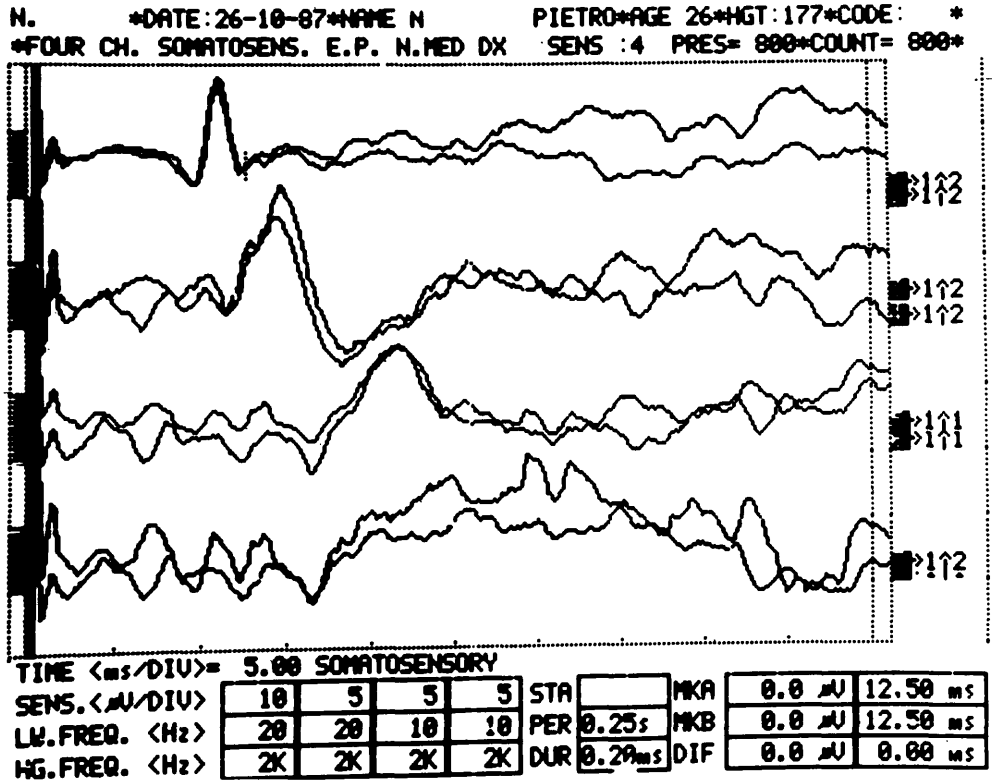

Figure 1—*SEPs at median nerve. N9: first trace stimulus at brachial plenux; N13: second trace stimulus at spinal; N20: third trace stimulus at contralateral cortex; N20′:fourth trace stimulus at omolateral cortex.*

ical); CATs were conducted with a computer-assisted system; and SEPs (Fig. 1) were measured with Basis Ote Biomedica Instruments and MEPs (Fig. 2) with Novametric magnetic stimulator. *F* waves were elicited by stimulating the median nerve at the wrist and recording from the APB muscle. SEPs were established by stimulating the median nerve at the wrist bilaterally from Erb's point (N9), C7 (N13), and the contralateral cortex (N20) and (N20′) omolateral cortex. In each patient, magnetic stimuli were given at the vertex at increasing intensities while the patient maintained a slight voluntary abduction of the first digit, ~5–10% of maximum force. The time difference between the motor cortex and cervix of the hand or forearm muscles represents the conduction velocity of the cortical-cervical cord motor neurons. We calculated the difference between these values (cortex-APB, C7-APB) to obtain the time of latency from C7 to the cortex. The intensity of the magnetic stimulation was enough to obtain a motor response with an amplitude equal to 80% of the supramaximal motor response at the wrist. During stimulation, a facilitation of 10% of the maximal contraction was made. Figure 2 shows MEPs at wrist, elbow, C7, and motor cortex.

Statistical analysis was performed by Student's *t* test and Pearson's test for the correlation between the different techniques. The significance level, in accordance with Bonferroni's correction for multiple comparisons, is adjusted for a minimum significance level ($P < 0.002$) (0.05/24; number of neurophysiological tests evaluated). We analyzed the percentage of impairment of MEPs, SEPs, SCVs, MCVs, CATs (2.5 percentile), and VPTs (97.5 percentile) compared with age-related values based on 200 healthy subjects (Table 3).

RESULTS— SCV of the sural nerve was statistically longer (45.6 ± 5.7 m/s) in diabetic patients compared with control subjects (52 ± 6.9 m/s) ($P < 0.001$), while MCV of the peroneal nerve in diabetic patients was only delayed (47 ± 3.3 m/s) but not statistically significant in comparison with control subjects (51 ± 4 m/s). No differences were found between the two groups regarding both VPT values (Table 1), evaluated at big toe and ankle, and CAT responses. SEP latencies at Erb's point were only prolonged in diabetic patients compared with control subjects, with the same alteration for the right arm (10.2 ± 0.74 vs. 9.27 ± 0.55 m/s) and the left arm (10.1 ± 0.73 vs. 9.23 ± 0.5 m/s). The MEP study also showed prolonged, but not statistically significant, latencies between point C7 and the homolateral APB muscle (right side: 12.5 ± 0.69 m/s in patients, 12.8 ± 0.46 m/s in control subjects; left side: 13.32 ± 0.96

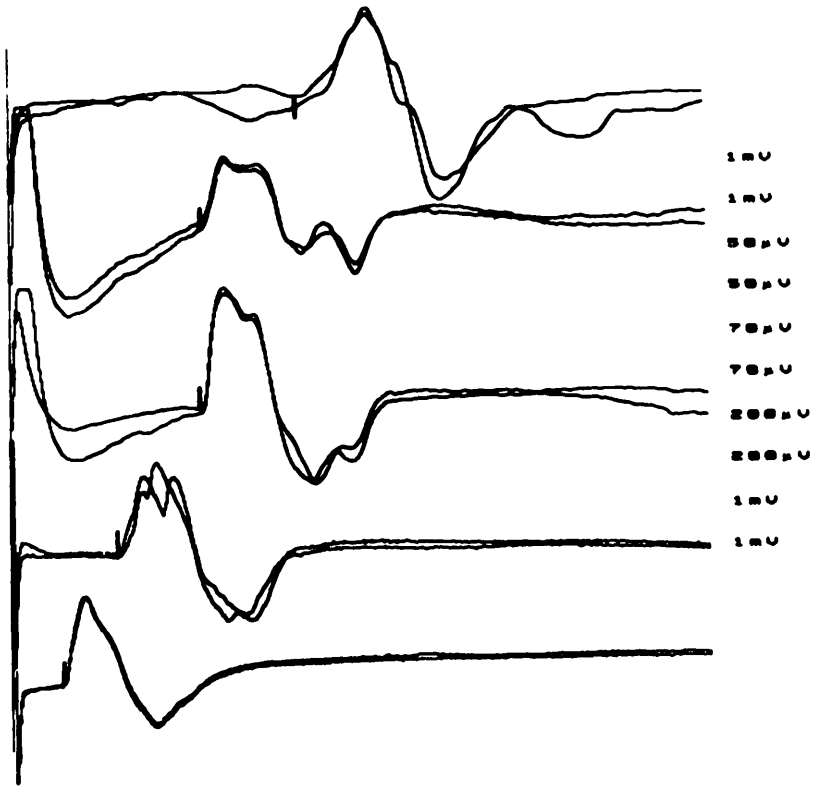

Figure 2—*MEPs recorded at APB. First trace: stimulation of median nerve at wrist; second trace: stimulation of median nerve at elbow; third trace: stimulation of median at Erb's point; fourth trace: stimulation of contralateral cortex.*

m/s in patients, 12.5 ± 0.69 m/s in control subjects). The correlations between the different techniques showed that MEP values C7–APB muscle correlated with those of SEPs at Erb's point ($r = 0.80$). MEP values exceeded the normal range (2.5 percentile in 7% of diabetic patients) when evaluated at the segment between the cortex and C7; and when evaluated at the segment between C7 and APB muscle, 50% of SEP-latency values were found to be impaired in 13% of diabetic patients at cortex, 40% at C7 point, and 60% at Erb's point. In addition, MCV of the peroneal nerve was abnormal in 46% of patients, and SCV of the sural nerve was abnormal in 40% of diabetic patients. VPT and CAT values were all within normal range.

Table 1—*MCVs, SCVs, VPTs, and CAT responses in diabetic patients and control subjects*

	Control subjects	Diabetic patients
n	10	15
MCV (m/s)	51 ± 4.0	47 ± 3.3
SCV (m/s)	52 ± 6.9	45 ± 5.7*
VPT (V)		
First finger	7.5 ± 1.2	8.0 ± 2.0
Ankle	6.5 ± 1.2	7.0 ± 1.5
CATs		
Lying-to-standing (30/15)	1.30 ± 0.14	1.31 ± 0.13
Standing-to-lying	1.16 ± 0.05	1.14 ± 0.06
Deep breathing	1.51 ± 0.24	1.50 ± 0.25
Postural hypotension	0 ± 10	0 ± 10
Valsalva manouver	2.10 ± 0.47	2.06 ± 0.28

Data are means ± SD. *$P < 0.001$.

Table 2—*SEPs and MEPs in type I diabetic patients and control subjects*

Sites studied	Control subjects	Diabetic patients
n	10	15
N20		
(C'3)	21 ± 1.3	22 ± 2
(C'4)	21 ± 1.4	22 ± 1.9
Central conduction time		
Right	8 ± 1.8	6.8 ± 0.6
Left	7.5 ± 2.1	8.3 ± 0.5
C7		
Right	13 ± 1.2	15 ± 1.0
Left	14 ± 1.5	15 ± 1.4
N9		
Right	9.3 ± 0.5	10 ± 0.7
Left	9.2 ± 0.5	10 ± 0.7
Cortex		
Left APB	19 ± 0.8	20 ± 1.0
Right APB	19 ± 1.1	20 ± 0.9
C7		
Right ABP	13 ± 0.5	14 ± 1.0
Left ABP	12 ± 0.7	13 ± 0.9
Central conduction time		
(C'3–C7)	6.3 ± 1.0	5.9 ± 0.7
(C'4–C7)	6.4 ± 0.8	6.3 ± 0.7
F wave	27 ± 1.6	29 ± 1.3

Data are means ± SD in m/s.

CONCLUSIONS — This study assesses the topography of the damage in the various segments of the nervous system with several different neurophysiological tests. Using Bonferroni's correction test (Tables 1 and 2), the whole test, except the data for SCV, proves to be statistically insignificant. However, the calculus of impairment in respect to normal

Table 3—*Frequency of abnormal neurophysiological parameter values in type I diabetic patients and control subjects*

Parameters	Frequency	
	Diabetic patients	Control subjects
SEPs		
C7–Cortex	13	0
Wrist–Cortex	25	0
Wrist–C7	40	0
Wrist–Erb's point	60	0
MEPs		
Cortex–C7	7	0
Cortex–ABP	28	0
C7–ABP	50	0
Nerve Conduction Velocity		
Peroneal motor	46	0
Sural sensory	40	0
VPT (big toe and external malleolus)	0	0
CATs	0	0

Data are %. CATs include Valsalva ratio, lying-to-standing, standing-to-lying, deep breathing, and postural hypotension.

range values (Table 3), when used as descriptive analysis, records the possible trend of nervous fiber damage, naturally keeping in mind that our results are limited because of the low number of patients. Interestingly, in studying very small groups of patients with diabetes duration <5 years and good metabolic control, the MEP techniques can show an impairment of 28–50% in peripheral sites as well as SEPs 40–60% and nerve conduction velocities 40–46%, with respect to normal values. Instead, the central conduction time, evaluated with MEPs (Cortex–C7) and SEPs (C7–Cortex) was found altered in 7 and 13% of the diabetic patients, respectively. Impairments of VPT and cardiovascular function were not found according to Maser et al. (8) and Ewing et al. (9). This evidence is quite important because it allows for a clear picture of how diffused and how early the onset of impairment of the nervous system could be in type I diabetic patients, as well as how different the percentage of damage could be in the different districts of the nervous system. The impairment of the central pathway could be due to the same causes of damage in peripheral nervous fibers or perhaps to other causes. However, the varying percentage of impairment of CNS and the peripheral nervous system is very difficult to explain; in fact, CNS cells may be less impaired than peripheral nervous system cells, presumably because the blood-brain barrier transport for glucose decreases from 44 to 25% and because GLUT1 has been found to be decreased by 77% in the brain capillaries (9). A minor glucose toxicity in CNS cells as compared with the point where this barrier is not found (peripheral nerves) could be hypothesized. The different percentage of impairment, evaluated by SEP and MEP techniques, between central and peripheral fibers could be explained by a minor activity of the polyol metabolic pathway via the aldose reductase pathway of the brain with respect to other tissues (10). Several episodes of hypoglycemia may occur in type I diabetic patients with good metabolic control, and relative cerebral hypoglycemia can occur in absence of clinical signs of hypoglycemia (11). Brain hypoglycemia may cause alterations of nervous cells (12). These current opinions could explain the early but less severe impairment in the CNS compared with the impairment of other nervous sites. In patients with normal metabolic control and normoglycemia during testing, our study clearly demonstrates that the damage is more evident in peripheral sites where hyperglycemia and the aldose reductase pathway are more active.

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