Early Detection of Neurological Involvement in IDDM and NIDDM

Multimodal Evoked Potentials Versus Metabolic Control

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Clarification of the extent and mechanisms of damage to the central nervous system in diabetes is a frontier of current neurological research. Our aim was to obtain ample electrophysiological documentation of possible neurological abnormalities in both insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetic patients with a short duration of disease and without overt complications, taking into account metabolic control. Group 1 comprised 11 IDDM patients, and group 2 included 14 NIDDM patients treated with diet alone; the duration of disease was <4 yr, and no concomitant clinical complications were present. Age- and sex-matched normal subjects formed groups 3 and 4. Pattern visual evoked potentials (VEP), brain stem auditory evoked potentials (BAEP), and somatosensory evoked potentials (SEP; after the stimulation of both median and tibial nerves) were recorded in all subjects, and metabolic control was evaluated in terms of glycemia and glycosylated hemoglobin. In group 1, significant abnormalities were found in the latency values of VEP, median SEP, and tibial SEP compared with control subjects. Similar latency abnormalities were shown in group 2 for VEP, median SEP, and tibial SEP values and for wave I latency of BAEP. Glycosylated hemoglobin values were correlated with BAEP and SEP abnormalities in many patients in both groups. Furthermore, in group 2, glycemic values correlated with SEP abnormalities. We therefore conclude that neurophysiological abnormalities are present at different levels in IDDM and NIDDM patients only a few years after clinical diagnosis and before the appearance of overt complications, and these abnormalities seem to be correlated with metabolic-control status. *Diabetes Care* 11:473–80, 1988

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Extensive electrophysiological documentation exists on the occurrence of complex nervous abnormalities at a peripheral level during the course of diabetes (1–4). A major role in this form of neuropathy has been attributed to alterations of the vasa nervorum, as documented by histological studies (5). However, other researchers have hypothesized the additional involvement of metabolic factors in the evolution of peripheral neuropathy (6–9).

In the past few years, growing attention has been focused on a more general involvement of the nervous system in diabetes, affecting not only the peripheral but also, more interestingly, the central nervous system (CNS) (10–18). These studies have revealed CNS abnormalities but have failed to show how and when these alterations occur. In fact, in most studies, patients were recruited regardless of duration or type of diabetes, presence of long-term complications, or metabolic-control status. Moreover, CNS function was evaluated with one or, at most, two methodological approaches, but no complete evaluation of multimodal evoked-potential recordings in the same diabetic patient has been reported (10,12,13,19,20).

The aim of this study was to obtain multimodal recordings of evoked potentials [visual (VEP), brain stem auditory (BAEP), and median and tibial somatosensory (SEP) evoked potentials] in both insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetic patients, with a negative neurological examination and with no other overt long-term complication, in an early phase of the disease. Metabolic control was determined by the evaluation of glycemia and glycosylated hemoglobin (HbA_{1c}) to verify the presence of possible correlations between electrophysiologic parameters and short- and medium-term metabolic and biochemical findings.

MATERIALS AND METHODS

Twenty-five diabetic patients were included in the study together with 40 normal control subjects. Patients and control subjects were divided into groups.

Group 1 comprised 11 IDDM patients (7 men, 4 women), aged 18–32 yr (mean ± SD 23.0 ± 4.7 yr), whose duration of diabetes was between 0.6 and 4 yr (mean 2.58 ± 1.3 yr). Mean values of glycemia and HbA_{1c} were 10.09 ± 4.63 mM (range 5–21 mM) and 9.48 ± 3.25% (range 5.5–15.7%), respectively.

Group 2 included 14 NIDDM patients (4 men, 10 women), aged 41–58 yr (mean 48.9 ± 8.5 yr), whose duration of disease was between 1 and 4 yr (mean 2.9 ± 1.44 yr). These patients were not receiving hypoglycemic therapy but were controlled solely through diet. In group 2, mean values of glycemia and HbA_{1c} were 8.21 ± 5.22 mM (range 4–24 mM) and 7.46 ± 2.04% (range 5.3–11%), respectively.

The criteria for selection of diabetic patients were *1*) clinical diagnosis of diabetes within the preceding 4 yr; *2*) absence of symptoms and signs suggestive of diabetic radiculopathy (21) and/or distal polyneuropathy (17,22) on the basis of history and clinical examination (the negative finding was confirmed by electromyography before other studies); *3*) absence of inflammatory, vascular, or neoplastic diseases at the level of the CNS and of severe spinal deformity; absence of nephropathy and pathological obesity; and normal ophthalmological (visual acuity, fundus oculi) and audiological (tonal audiometry) tests; and *4*) no pregnancy.

None of the patients was receiving psychoactive drugs or was in a state of hypoglycemia or ketoacidosis at the time of performing electrophysiological tests.

Group 3 comprised 20 normal control subjects chosen with age (17–33 yr, mean 22.9 ± 4.3 yr) and sex (13 men, 7 women) distribution comparable to that of group 1 patients. Group 4 consisted of 20 normal control subjects comparable in age (40–61 yr, mean 51.0 ± 6.4 yr) and sex (6 men, 14 women) to patients in group 2.

Neurophysiological methods. VEP recordings were carried out with a checkerboard pattern reversal on a television monitor, subtending an angle of 17°. The spatial checkerboard frequency was 0.78 cycle/deg, and the temporal frequency of pattern reversal was 2 Hz. The mean luminance was 60 cd/m^2, and the contrast between dark and bright checks was 50%. The active needle electrode was placed 5 cm above the inion along the midline, the reference electrode was at F_z, and a ground electrode was placed on the mastoid. Left and right monocular recordings were performed with an average of 128 signals (analysis time 500 ms).

BAEP recordings were performed with an acoustic stimulus in the form of a click (unfiltered square waves of 0.120 ms duration with alternating polarity and a frequency of 10 Hz). The stimulus was transmitted monaurally at an intensity of 80-dB hearing level (HL) through earphones. Continuous white noise at an intensity of 60-dB HL was used to mask the unstimulated ear. The active needle electrode was placed at the vertex, the reference electrode on the mastoid ipsilateral to the stimulated ear, and the ground contralateral. An average of 2048 signals were performed (analysis time 10 ms).

SEP recordings were obtained with an electrical stimulus (a square wave of 0.1–0.3 ms duration and 7 Hz frequency) with surface electrodes (the proximal cathode was placed 3 cm from the anode) on the median nerve at the wrist and subsequently on the tibial nerve at the ankle. The intensity of the stimulus, at a constant current (mA), was regulated to produce a twitch in the thumb and the dorsiflexion of the toes.

The test was performed consecutively on each side. The bioelectrical activity was assessed with Ag/AgCl-cup electrodes. The impedance of the electrodes was maintained under 6 KΩ. While stimulating the upper limb, exploratory electrodes were placed in the mediocleaveal area (Erb), in the cervical area (C_7), and in the parietal area contralateral to the stimulation (C_3^1 or C_4^1: 2 cm posterior to C_3 or C_4, according to the International 10–20 System of EEG electrode placement; 23). A common reference electrode and a ground electrode were placed at the level of the earlobe (A_1 or A_2) and on the arm contralateral and ipsilateral to the stimulated side, respectively. Five hundred twelve stimuli were emitted during each test (analysis time 50 ms). During stimulation of the lower limb, electrodes were placed in relation to the cauda equina (L_3-L_2) to the thoracic region (T_{12}-T_{11}), and to the scalp (2 cm behind C_z: C_Z^1 and F_{pz}). A ground electrode was placed on the sacral region. Analysis time was 50–100 ms, and an average of 2048 signals were performed in each test.

All the bioelectrical signals were filtered (band pass: VEP 0.3–125 Hz, BAEP 100–3000 Hz, SEP 10–1500 Hz, slope 12 dB/octave), amplified (BAEP 10 μV/division, VEP and SEP 20 μV/division), and sent to a Medelec ER94a sensor for averaging; the system was equipped with a mechanism for the automatic rejection of artifacts. Each trace was plotted on paper with an X-Y 7470A Hewlett-Packard plotter and was repeated at least twice to verify reproducibility.

Analysis of recordings. The following parameters were taken into consideration:

VEP—the latency of the positive (P) wave with the highest voltage (P100, which represents the response of the visual cortex to retinal stimulation) (24,25).

BAEP—the absolute latency of wave I (the expression of the function of the acoustic nerve); interpeak latency (IPL) values of waves I–III [conduction time (CT) from the acoustic nerve to the pons]; III–V IPL (central CT from the pons to the midbrain); I–V IPL (expression of the activity of the auditory pathways from the periphery to the midbrain) (26,27).

Median SEP—wrist-Erb conduction velocity (CV) (representative of CV along the peripheral nerve fibers from the wrist to the brachial plexus); interval between Erb-N_{13} (the CT across the brachial plexus and the cervical

cord), N_{13}–N_{20} interval (the CT from the cervical cord/lower brain stem lemniscal pathways to the cortex), and Erb–N_{20} transit time (the CT from the brachial plexus to the cortex) (28,29).

Tibial SEP—ankle-L_3 CV (along the peripheral nervous fibers from the ankle to the cauda equina); propagation velocity L_3–C_Z^1 and central CV T_{12}-C_Z^1 [CV with which the nerve impulse is carried along the afferent somatosensory pathways from the cauda equina (L_3) and from the spinal cord (T_{12}) to the cortex (C_Z^1), respectively] (30,31).

The limit between normal and pathological values for electrophysiological findings was taken as the mean ± 3SD of a reference group of normal subjects of comparable age and sex chosen by our unit to statistically represent the normal population. Evoked potentials were considered pathological if the peak latency (VEP P100) and interpeak intervals (BAEP I–III, III–V, I–V; median SEP Erb-N_{13}, N_{13}-N_{20}, Erb-N_{20}) were >3SD above the mean values of control subjects. In addition, CVs (median SEP: wrist-Erb; tibial SEP: ankle-L_3, L_3-C_Z^1, and T_{12}-C_Z^1) were considered pathological if they were 3SD less than the normal averages (32).

Other methods. A blood sample to measure levels of glycemia and HbA_{1c} was collected from each patient in the morning while fasting. HbA_{1c} was assayed by ion-exchange chromatography, with 7.3% as the upper limit of the normal range.

Statistical analysis. The unrelated two-tailed *t* test comparing ipsilateral electrophysiologic values was used. Pearson's *r* as product-moment correlation was used to evaluate the statistical relationship between electrophysiological and serum (glycemia and HbA_{1c}) findings.

RESULTS

VEP recordings. A pathologic increase was found in the latency of the P100 wave in two patients in group 1 (unilateral in 1 case) and in three patients in group 2 (unilateral in 2 cases) (Tables 1 and 2). A statistically significant increase in the average values of the P100 latency was observed in both groups 1 and 2 compared with the corresponding control groups (Table 3). No clear correlation between the P100 latency with glycemia and HbA_{1c} was present in either group of patients (Table 4).

BAEP recordings. BAEP interpeak latencies were pathological in one patient in group 1 (increase of III–V IPL unilaterally and of I–V IPL bilaterally) and in two patients in group 2 (increase of III–V IPL unilaterally) (Tables 1 and 2). A statistically significant increase in the absolute latency of wave I was observed in group 2 compared with the control group (Table 3). No statistically significant difference was found when the mean values of the I–III, III–V, and I–V IPLs in either group of patients were compared with the respective control groups (Table 3).

A positive correlation with HbA_{1c} but not with single glycemic tests was found at I–III and III–V IPLs in group 1 and at I–III IPL in group 2 (Table 4).

Median SEP recordings. Although no patient presented a peripheral CV <3SD from normal levels, median SEP recordings were pathological in one patient in group 1 (unilateral increase in the interval Erb-N_{13}) and in three patients in group 2 (2 patients showed a pathologic unilateral interval Erb-N_{13}, and 1 showed an abnormal unilateral increase in the intervals Erb-N_{13}, N_{13}-N_{20}, and Erb-N_{20}) (Tables 1 and 2).

The wrist-Erb CV was significantly decreased in both groups of patients compared with the control groups (Table 3). Mean values of the interval Erb-N_{13} in group 2 and the interval Erb-N_{20} in group 1 were significantly increased compared with the control groups (Table 3). HbA_{1c} levels, but not glycemic values, were correlated with peripheral wrist-Erb CV in group 1 (Table 4), whereas HbA_{1c} was correlated with the interval N_{13}-N_{20} and, together with glycemic values, with the intervals Erb-N_{13} and Erb-N_{20} in group 2 (Table 4).

Tibial SEP recordings. Although no individual patient presented a reduction in peripheral CV <3SD from normal levels, two patients in group 1 revealed a pathologic reduction of the central CV T_{12}-C_Z^1 (unilateral in 1 case) (Tables 1 and 2). Four patients in group 2 showed a reduced propagation velocity, L_3-C_Z^1 and/or central CV T_{12}-C_Z^1 (unilateral in 3 cases and bilateral in 1 case) (Table 2).

A statistically significant reduction was observed in the peripheral CV in both groups 1 and 2 compared with the control groups (Table 3). Statistically significant decreases were also found relating to the propagation velocity L_3-C_Z^1 and the central CV T_{12}-C_Z^1 in both groups (Table 3). A correlation was present between peripheral CV and HbA_{1c} in group 1, whereas the propagation ve-

TABLE 1
Comparison of evoked-response alterations in diabetic patients

		Visual evoked potential		Brain stem auditory evoked potential		Median somatosensory evoked potential		Tibial somatosensory evoked potential		Multimodal evoked potentials	
	n	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Group 1	11	2	18.2	1	9.1	1	9.1	2	18.2	4	36.4
Group 2	14	3	21.4	2	14.3	3	21.4	4	28.6	10	71.4

TABLE 2
Tabulation of diabetic patients with electrophysiological abnormalities

	Case no.	Side	Visual evoked potential P100	Brain stem auditory evoked potential			Median somatosensory evoked potential				Tibial somatosensory evoked potential		
				I–III	III–V	I–V	Wrist-Erb	Erb-N_{13}	N_{13}-N_{20}	Erb-N_{20}	Ankle-L_3	L_3-C_z'	T_{12}-C_z'
Group 1	1	Right	108	2.08	1.96	4.04	68.4	5.6*	5.8	11.4	59.3	33.1	33.1
		Left	112	1.96	2.16	4.20	68.4	4.6	6.2	10.8	56.1	32.6	32.0
	4	Right	118*	2.28	2.20*	4.48*	70.7	4.2	6.6	10.8	57.9	26.9	25.4
		Left	118*	2.32	2.16	4.48*	73.7	4.6	6.4	11.0	58.4	27.8	26.1
	6	Right	102	2.08	1.52	3.60	75.0	4.0	5.8	9.8	65.4	24.5	22.4*
		Left	108	2.20	1.60	3.80	72.2	4.0	5.8	9.8	66.0	25.4	23.3*
	10	Right	118*	2.12	1.80	3.92	70.2	4.4	6.0	10.4	62.1	27.8	28.9
		Left	112	2.20	1.68	3.88	67.8	4.2	5.6	9.8	58.1	25.2	23.1*
Normal values (mean ± SD)			105.4 ± 3.5	2.09 ± 0.12	1.79 ± 0.13	3.88 ± 0.17	72.3 ± 3.6	4.32 ± 0.4	6.02 ± 0.5	10.3 ± 0.5	61.8 ± 3.6	30.8 ± 2.2	29.4 ± 2.0
Group 2	2	Right	112	2.08	1.92	4.00	67.8	5.0	6.6	11.6	53.8	23.5*	22.3*
		Left	116	2.08	1.80	3.88	66.6	5.4	5.8	11.2	55.0	31.3	29.8
	3	Right	120*	2.20	1.80	4.00	63.8	4.0	6.2	10.2	57.3	26.3	25.4
		Left	114	2.20	2.12	4.32	67.8	4.6	5.6	10.2	56.1	26.6	23.6
	5	Right	106	2.04	2.20	4.24	72.2	5.8*	5.0	10.8	62.0	28.5	27.9
		Left	108	1.92	2.12	4.04	69.7	4.4	5.8	10.2	60.8	29.5	29.1
	6	Right	116	2.20	1.92	4.12	65.0	4.8	6.6	11.4	58.3	26.3	19.8*
		Left	120*	2.20	1.88	4.08	67.9	4.8	6.4	11.2	56.1	26.6	19.8*
	7	Right	110	2.02	2.26*	4.28	67.5	5.2	6.0	11.2	59.2	24.7	23.7
		Left	110	2.28	1.92	4.20	68.2	4.8	6.0	10.8	57.8	27.5	25.3
	9	Right	110	2.08	2.08	4.16	70.8	5.2	5.2	10.4	56.4	25.4	25.4
		Left	108	2.16	2.24*	4.40	72.8	5.2	5.6	10.8	55.7	24.1	23.6
	10	Right	112	2.08	1.56	3.64	69.3	5.8*	6.0	11.8	60.0	28.2	27.6
		Left	116	2.28	1.64	3.92	68.1	4.8	6.2	11.0	60.8	26.1	24.8
	12	Right	108	2.04	1.96	4.00	63.6	4.4	5.4	9.8	57.8	30.1	28.5
		Left	110	2.08	1.84	3.92	66.6	4.4	5.8	10.2	57.0	28.5	21.2*
	13	Right	120*	2.20	2.08	4.28	66.3	5.0	6.6	11.6	54.7	28.4	26.8
		Left	126*	2.00	2.00	4.00	65.3	4.6	7.0	11.6	54.6	27.5	26.3
	14	Right	108	2.32	2.04	4.36	65.4	5.8*	7.8*	13.6*	62.5	22.4*	25.9
		Left	112	2.16	2.20	4.36	62.5	5.4	6.0	11.4	58.1	24.1	22.8
Normal values (mean ± SD)			108.1 ± 3.0	2.17 ± 0.09	1.90 ± 0.10	4.06 ± 0.12	69.2 ± 2.6	4.74 ± 0.3	6.09 ± 0.4	10.8 ± 0.4	59.7 ± 2.5	30.2 ± 2.1	28.6 ± 2.0

Values are in milliseconds (P100; I–III, III–V, I–V IPLs; Erb-N_{13}, N_{13}-N_{20}, Erb-N_{20}) and in meters per second (wrist-Erb; ankle-L_3, L_3-C_z', T_{12}-C_z').
*Pathologic value.

TABLE 3
Evoked-potential data in diabetic patients and normal control subjects

	Side	Visual evoked potential	Brain stem auditory evoked potential				Median somatosensory evoked potential			Tibial somatosensory evoked potential		
		P100	Wave I	I–III	III–V	I–V	Wrist-Erb	Erb-N_{13}	N_{13}-N_{20}	Erb-N_{20}	Ankle-L_3	L_3-C_Z^1	T_{12}-C_Z^1
Group 1 (n = 11)	Right	109.4 ± 5.7*	1.61 ± 0.06	2.17 ± 0.12	1.83 ± 0.20	4.00 ± 0.23	68.7 ± 3.6§	4.72 ± 0.5	6.05 ± 0.5	10.8 ± 0.7§	58.3 ± 5.0§	27.5 ± 2.4†	26.6 ± 2.9‡
	Left	111.4 ± 3.6†	1.63 ± 0.08	2.14 ± 0.20	1.85 ± 0.23	4.00 ± 0.20	69.0 ± 3.4‡	4.40 ± 0.2	6.07 ± 0.3	10.5 ± 0.4	57.2 ± 5.1‡	27.6 ± 2.7‡	26.4 ± 3.1‡
Group 3 (n = 20)	Right	104.7 ± 4.1	1.61 ± 0.05	2.09 ± 0.11	1.78 ± 0.11	3.87 ± 0.16	71.8 ± 3.8	4.34 ± 0.5	6.03 ± 0.5	10.4 ± 0.5	61.7 ± 3.4	30.8 ± 2.2	29.6 ± 2.0
	Left	106.0 ± 2.6	1.62 ± 0.07	2.09 ± 0.14	1.80 ± 0.15	3.89 ± 0.19	72.7 ± 3.4	4.30 ± 0.3	6.01 ± 0.4	10.3 ± 0.5	61.9 ± 3.9	30.7 ± 2.3	29.2 ± 2.1
Group 2 (n = 14)	Right	111.6 ± 4.7‡	1.67 ± 0.13	2.13 ± 0.10	1.95 ± 0.19	4.08 ± 0.20	67.3 ± 2.5§	5.04 ± 0.4§	6.08 ± 0.7	11.1 ± 0.9	57.8 ± 2.6*	26.5 ± 2.2†	25.4 ± 2.4†
	Left	112.4 ± 5.8*	1.74 ± 0.13‡	2.13 ± 0.12	1.94 ± 0.18	4.08 ± 0.21	67.6 ± 2.5	4.87 ± 0.3	6.00 ± 0.5	10.9 ± 0.5	56.4 ± 2.6‡	27.2 ± 2.0†	25.1 ± 2.8†
Group 4 (n = 20)	Right	107.8 ± 2.6	1.62 ± 0.04	2.16 ± 0.09	1.90 ± 0.09	4.05 ± 0.11	69.2 ± 2.6	4.78 ± 0.2	5.97 ± 0.4	10.7 ± 0.4	60.2 ± 2.8	30.2 ± 1.9	28.7 ± 1.9
	Left	108.5 ± 3.4	1.63 ± 0.04	2.17 ± 0.09	1.89 ± 0.12	4.07 ± 0.12	69.2 ± 2.7	4.70 ± 0.3	6.21 ± 0.4	10.9 ± 0.4	59.1 ± 2.1	30.2 ± 2.3	28.4 ± 2.1

Values are means ± SD in milliseconds (P100; I–III, III–V, I–V IPLs; Erb-N_{13}, N_{13}-N_{20}, Erb-N_{20}) and in meters per second (wrist-Erb; ankle-L_3, L_3-C_Z^1, T_{12}-C_Z^1).
*P < .02; †P < .001; ‡P < .01; §P < .05.

locity L_3-C_Z^1 was correlated with both glycemia and HbA_{1c} in group 2 (Table 4).

Overall analysis. Of the patients in groups 1 and 2, 36.4 and 71.4%, respectively, revealed one or more abnormalities in the electrophysiological tests (Table 1).

DISCUSSION

The existence of damage at the level of the CNS limited to IDDM has previously been demonstrated by a few authors with different morphological and sectorial neurophysiological approaches. However, although several studies have confirmed the presence of foci of demyelinization, axonal degeneration, and even processes of vasculopathy (to the extent that the terms *diabetic encephalopathy* and *diabetic myelopathy* have been coined), the pathogenetic mechanisms have not yet been identified (33–38).

In this study the presence of multiple and different neurophysiological abnormalities, as detected by means of multimodal electrophysiological evaluation, has been shown not only in IDDM, but, interestingly, also in NIDDM patients. Surprisingly, these abnormalities are present only a few years after diagnosis and well before the appearance of overt pathologic manifestations. Thus, the abnormalities are not typical of long-standing complicated forms of the disease but appear to be correlated with the degree of diabetic metabolic imbalance.

By using a multimodal neurophysiological approach instead of single-test evaluations, it was possible to depict a broader and more complete map of the possible abnormalities. In fact, the electrophysiologic responses obtained with the three methods (VEP, BAEP, and SEP) were not always altered contemporaneously in the same patient.

Of the neurophysiologic abnormalities detected by this methodological approach, pathologic tibial SEP values were found in many cases, revealing a significant reduction both in peripheral CV (ankle-L_3) and in the propagation velocity along the sensory pathways from the cauda equina (L_3-C_Z^1) and from the posterior columns of the spinal cord to the scalp (T_{12}-C_Z^1). The two abnormalities were not always associated in the same subject. These results may be explained by nerve vulnerability differences in the individual or by the greater anatomical length of this conduction system. Alternatively, they may simply reflect the model of central-distal axonopathy of toxic metabolic neuropathy, in which there is an earlier involvement of the spinal cord and distal segments of peripheral nerves (39–41). These electrophysiological data are in agreement with the anatomopathological findings of Slager (38), who reports that lesions of the spinal cord occur in diabetic patients.

The significant reduction in the wrist-Erb CV in both groups along with the increase of absolute latency of wave I of BAEP recordings in NIDDM patients further

TABLE 4
Pearson's correlations between electrophysiological and biochemical data in diabetic patients

	Visual evoked potential	Brain stem auditory evoked potential				Median somatosensory evoked potential				Tibial somatosensory evoked potential		
	P100	Wave I	I–III	III–V	I–V	Wrist-Erb	Erb-N_{13}	N_{13}-N_{20}	Erb-N_{20}	Ankle-L_3	L_3-C_Z^1	T_{12}-C_Z^1
Group 1												
Glycemia	.063	.192	.320	−.030	.210	−.413	.377	−.161	.171	−.364	.067	.233
HbA_{1c}	−.312	−.066	.422*	.650†	−.292	−.471‡	.113	.191	.222	−.445‡	−.292	−.191
Group 2												
Glycemia	−.001	−.012	.199	−.327	−.186	−.347	.427‡	.384	.561†	.305	−.566†	−.125
HbA_{1c}	−.078	−.274	−.603§	−.090	.254	−.287	.464‡	.471‡	.670§	.334	−.397‡	−.093

*P = .05; †P < .01; ‡P < .05; §P < .001.

confirms the involvement of the peripheral structures during diabetes. However, the absence of significant increases in the interpeak latencies in IDDM and NIDDM patients is an overall indication of the lesser involvement of the brain stem compared with other nerve structures during the early phases of diabetes. These results are also confirmed by the fact that there was no significant increase in the interval N_{13}-N_{20} with median SEP. However, these data do not exclude the occasional presence of anatomofunctional damage to the brain stem structures, as demonstrated by the pathologic increase of III–V IPL in some of the cases examined.

During the course of diabetes there is also an evident involvement of the optic pathways, as shown by VEP recordings; however, given the complexity of the phenomena involved in the genesis of this potential, it is not possible to identify the lesion site.

Interestingly, the electrophysiologic responses frequently appeared to be unilaterally pathological. This is probably due to the presence of general factors (e.g., neurotoxins or false neurotransmitters), which, by asserting a negative influence on a focus of demyelinization and/or axonal degeneration, may contribute to the production of a defective segmentary conduction of the nervous impulse, as observed in other metabolic diseases (42).

The percentages of electrophysiologic alterations observed in this study are not readily comparable to those published in earlier reports because of the duration of disease considered by other authors. Also, most earlier studies were not performed with multimodal neurophysiological tests and at times were not carried out extensively on both sides of the subjects examined. Finally, comparison is limited by the different criteria used in the evaluation of electrophysiological findings (10, 12,13,19,20).

The presence of neurophysiologic abnormalities in both IDDM and NIDDM patients, the latter treated with diet alone, is intriguing. Even if the duration of disease in NIDDM is longer because of the insidious onset, factors other than the pathogenetic mechanisms differentiating IDDM from NIDDM or the severe lack of endogenous insulin appear to play a major role in this neurologic disorder.

Other interesting points may be raised by the evidence of clear neurophysiologic abnormalities in diabetes of short duration. The mechanisms involved must interfere chronically and progressively with some crucial aspect of the nervous function to produce such an early effect. That this damage is precocious and primary is also shown by the absence of any other clinical complication or pathological association in the patients studied.

The various correlations observed between electrophysiological data and metabolic control indicate that the latter may play an important pathogenetic role in the neurophysiologic abnormalities that occur during the early phases of diabetes mellitus. In both types of diabetes mellitus, correlations with metabolic control were found at some peripheral and central levels of the nervous system. The stronger association with HbA_{1c} than with single glycemic tests suggests that the medium- to long-term metabolic derangement influences neurologic function. Nevertheless, the correlation confirms the complexity of the mechanisms leading to abnormal evoked response. Increasing evidence suggests that the accumulation of glucose substrate, as a consequence of the relative lack of insulin, increases the aldose reductase activity (43,44). The increased enzyme activity of the alternate polyol pathway at different levels, including kidney, vessel walls, and retina but particularly in the nerve complex metabolism, may slowly and progressively impair neurologic functions; this is revealed first by an altered transmission and later by a more complex clinical manifestation.

Our findings reinforce that multimodal electrophysiological analysis is a sensitive noninvasive tool to detect initial neurophysiologic abnormalities in clinically silent diabetic patients. The statistical correlation between neurophysiologic abnormalities and metabolic control highlights the potential value of this combined approach in long-term monitoring of the early stages of diabetic neurologic damage.

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