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BRAINSTEM AUDITORY EVOKED POTENTIAL, VISUAL EVOKED POTENTIAL AND NERVE CONDUCTION VELOCITY AND THEIR RELATION WITH HbA_{1c} AND β_2 MICROGLOBULIN IN CHILDREN WITH INSULIN DEPENDENT DIABETES MELLITUS*

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SUMMARY: Akıncı A, Deda G, Karagöl U, Teziç T. (Dr. Sami Ulus Children's Hospital, Ankara, Turkey). Brainstem auditory evoked potential, visual evoked potential and nerve conduction velocity and their relation with HbA_{1c} and β_2 microglobulin in children with insulin dependent diabetes mellitus. Turk J Pediatr 1994; 36: 279-287.

Brain stem auditory evoked response (BAER), visual evoked response (VER) and nerve conduction velocities (NCV) were studied in 18 insulin-dependent diabetic children between the ages of 3.5 and 16 years (mean 9.0 ± 3.2 years). The results were compared with those of age-matched controls. The VER latencies of the diabetic children in the right eye and left eye were significantly prolonged when compared with the control group. NCV of n.peroneus and the latency of sensorial n.medianus were significantly impaired when compared with the control group.

Although the latencies of waves III, IV and V of the right ear and the interpeak latencies of I-III, I-V, III-V of both ears were prolonged, the comparison with the control group was not significant. The β_2 microglobulin levels of the diabetic patients were significantly higher than those of the control group. There was a positive correlation between the β_2 microglobulin and the BAER interpeak latencies of wave III-V in both ears ($r: 0.51$ $p < 0.01$). There was also a positive correlation between NCVs of n.peroneus and n.medianus (motor and sensorial) with β_2 microglobulin ($r: 0.52$ $p < 0.01$) and between VER latencies ($r: 0.52$ $p < 0.01$) of both eyes separately.

In our study the prolonged latencies of VER and BAER were detected in the absence of clinical abnormalities in visual and hearing systems. Due to our findings, we conclude that prolongation of latencies of VER and BAER are mostly the first signs of central nervous system (CNS) involvement in insulin-dependent diabetes, and the procedures are easy to perform as well as harmless to patients. *Key words: brainstem auditory evoked potential, visual evoked potential, HbA_{1c}, β_2-microglobulin, insulin dependent diabetes mellitus.*

Neuropathy is the most precocious and frequent complication of diabetes mellitus. All the clinical and diagnostic studies on diabetic neuropathy have concerned only peripheral and autonomic nerve impairment. Very few data exist on the involvement of the central nervous system (CNS) in diabetes, especially in children[1].

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Although the true incidence of diabetic neuropathy has never been rigorously established in a population-based study, the prevalence of neuropathy appears to correlate with the duration and severity of hyperglycemia in both insulin-dependent (IDDM) and non-insulin-dependent diabetes mellitus[2]. The pathogenesis of diabetic neuropathy remains largely unresolved. The suggested pathogenetic scheme is summarized in Fig. 1[3]. Hyperglycemia generates rheologic changes to increase endoneural vascular resistance and reduce nerve blood flow (NBF). It also reduces the transport of myoinositol (MI) into nerve and increases nerve glucose, fructose and sorbitol by activating the polyol pathway. The possible effect of hyperglycemia on inducing capillary changes is speculative but of crucial importance. Similarly speculative are other mechanisms (such as genetic and immune mechanisms) of capillary damage. Endoneural hypoxia is secondary to NBF reduction and increased endoneural vascular resistance. Once hypoxia is established, it is postulated that it may start a vicious cycle of further capillary damage and escalating hypoxia. Endoneural hypoxia may impair axonal transport of structural proteins and impair nerve Na-K-ATPase activity. Both mechanisms are postulated to reduce nerve conduction velocity, the former by inducing axonal atrophy and the latter by reducing membrane current density. Nerve MI is also suggested to cause Na-K-ATPase hypoactivity[3] (Fig. 1).

Our investigation aimed to evaluate the degree of early alterations of the optic pathways and hearing system detected by visual evoked response (VER) and

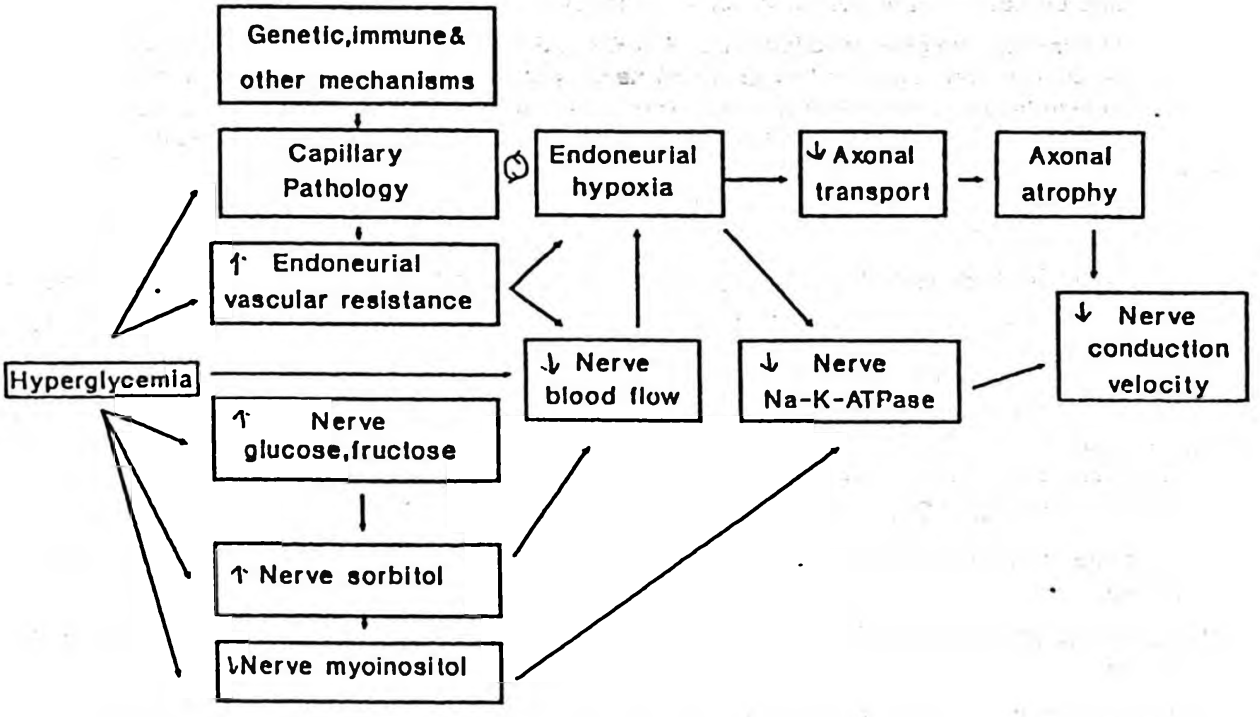

Fig. 1: Suggested pathogenesis of diabetic neuropathy.

brainstem auditory evoked response (BAER) techniques as well as any correlation between VER, BAER and clinical and metabolic parameters of the disease and paraclinical parameters of polyneuropathy in a population of diabetic children without retinopathy or any clinical hearing loss.

Material and Methods

We studied 18 diabetic patients (10 boys, 8 girls), mean age 9.0 ± 3.2 years (range 3.5-16 years) with a mean duration of disease since diagnosis being 38.3 ± 13.1 months (range 20-59 months). All patients were under conventional insulin therapy, regular insulin + NPH insulin twice per day. The mean insulin dosage was 0.6 ± 0.25 IU / Kg / day (0.4-1.1).

The control of diabetes were investigated by regular measurements of HbA_{1c} and blood glucose. None of the patients had visual or hearing impairment.

The control group consisted of nine healthy subjects for BAER with a mean age of 7.2 ± 2.8 years (range of three to 12 years), 10 healthy subjects for VER with a mean age of 7.6 ± 2.8 years (range of three to 12 years) and 16 healthy subjects for nerve conduction velocities (NCVs) of n.peroneus, n.medianus and the latency of n.medianus (sensorial) with a mean age of 8.2 ± 2.83 years (range of 2.5-12 years).

HbA_{1c} and β_2 microglobulin were also studied both in diabetics and in the 18 healthy subjects.

The patients were evaluated for retinopathy by angiography and none displayed evidence of it.

Evoked potential studies:

Visual evoked potentials were recorded in a dark room. Both eyes were stimulated separately and binocularly at full field by a checkboard pattern reversal with a 16 x 16 mm check size at 1 Hz. The amplitude and latency of the positive wave (P100) were calculated.

Brainstem auditory evoked responses were recorded in a shielded, sound-attenuated room with stimulus at an intensity of 90 decibels normal hearing level (nHL) in both ears at 10 cps. During BAER recording, silver surface electrodes were applied at the vertex (explorer), the forehead (ground) and the auricular lobe (common) with standard electrode paste as conductive medium. Acoustic alternating transients were presented monoaurally through shielded earphones. The computer average of 2000 clicks was obtained for each ear. Wave I through V individual latencies, and interpeak latencies between waves I-III, I-V and III-V were measured. The latency was evaluated from the electrical onset of the click at the earphone to the peak of the wave. Wave I latency

values are considered to be the index of peripheral transmission, while wave I-V interpeak latency represents an index of central transmission time. Wave I is generated primarily by the portion of nerve VIII that is contiguous with the spiral ganglion in the mastoid bone, while wave II represents cochlear nuclei (pons), wave III represents superior olivary, wave IV represents lateral lemniscus and wave V represents inferior colliculus (midbrain)[4].

Motor nerve conduction velocities were evaluated from n.peroneus and n.medianus. Sensorial latency of n.medianus was also detected using a Nihon Kohden Neuropack 2 device according to Thompson[5].

β_2 microglobulin was measured by the radioimmunoassay method with Pharmacia double antibody.

HbA_{1c} was studied with chromatographic spectrophotometry (Biosystem, ion-exchange).

Statistical analysis: Student's t test, paired t test and correlation analyses were used.

Results

There was no significant difference between the ages of diabetic patients and the control groups ($p > 0.05$).

Table I: Latencies of Brainstem Auditory Evoked Response (msec)

Wave	Diabetic Patients	Control Group	
Left Ear	90 dB	90 dB	P
I	1.41 + 0.28	1.76 + 0.40	> 0.05
II	2.47 + 0.23	2.75 + 0.49	> 0.05
III	3.63 + 0.32	3.96 + 0.45	> 0.05
IV	4.80 + 0.33	5.12 + 0.42	> 0.05
V	5.78 + 0.44	5.84 + 0.51	> 0.05
I-III	2.26 + 0.20	2.19 + 0.14	> 0.05
III-V	2.05 + 0.48	1.83 + 0.21	> 0.05
I-V	4.30 + 0.44	4.07 + 0.19	> 0.05
Right Ear			
I	1.56 + 0.27	1.54 + 0.51	> 0.05
II	2.82 + 0.20	2.73 + 0.59	> 0.05
III	3.93 + 0.46	3.73 + 0.59	> 0.05
IV	5.05 + 0.38	4.70 + 0.60	> 0.05
V	6.00 + 0.58	5.71 + 0.80	> 0.05
I-III	2.36 + 0.52	2.23 + 0.44	> 0.05
III-V	2.10 + 0.18	1.97 + 0.47	> 0.05
I-V	4.47 + 0.62	4.16 + 0.69	> 0.05

In our study the latencies of waves III, IV and V of the right ear and the I-V, I-III, III-V interpeak latencies of both ears were prolonged in the diabetic patients

but were not statistically significant when compared with the control group. Pattern-shift visual evoked responses (PSVER).

Table II: Visual Evoked Potentials

	Diabetic Patients	Control Group	P
P100 latencies (ms.)			
Left eye	113.83 + 10.09	93.47 + 4.31	< 0.001
Right eye	111.41 + 10.72	94.17 + 4.11	< 0.001
Binocular	109.92 + 16.32	108 + 6	> 0.05
Amplitudes (uV)			
Left eye	11.12 + 4.40	6.9 + 2.3	
Right eye	10.90 + 3.75	6.6 + 2.3	

There was a significant increase in the P100 latencies of the right and left eye separately ($p < 0.01$) (Fig. 2). With binocular stimulation there was no significant increase in P100 latency ($p > 0.05$). None of these patients had retinopathy. There was no correlation between PSVEP and age, duration of diabetes, or HbA_{1c} using correlation analysis, but there was a positive correlation between β_2 microglobulin and the P100 latencies (Fig. 3) (r: 0.52, $p < 0.01$) of both eyes separately; there was also a positive correlation between motor nerve conduction velocity of n.peroneus and P100 latency of the left eye.

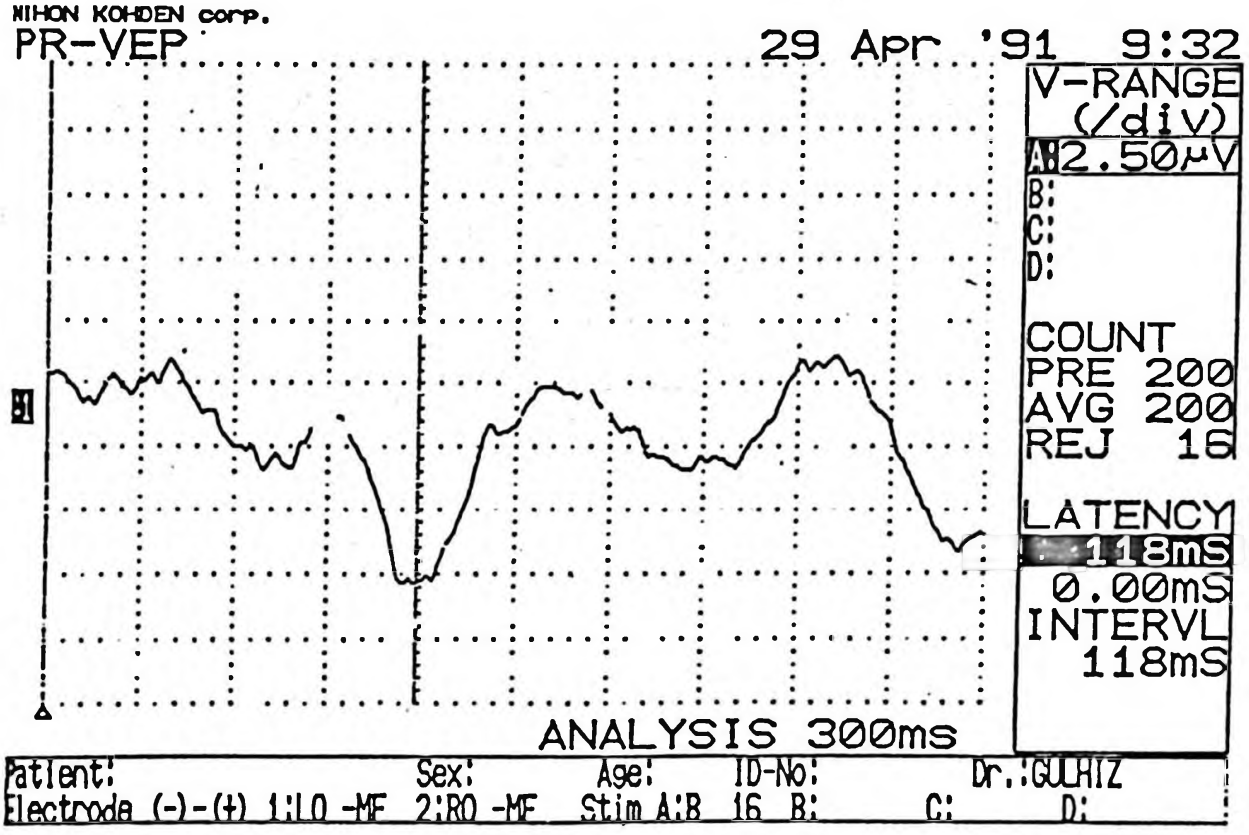

Fig. 2: VER Recorded From a Diabetic Patient.

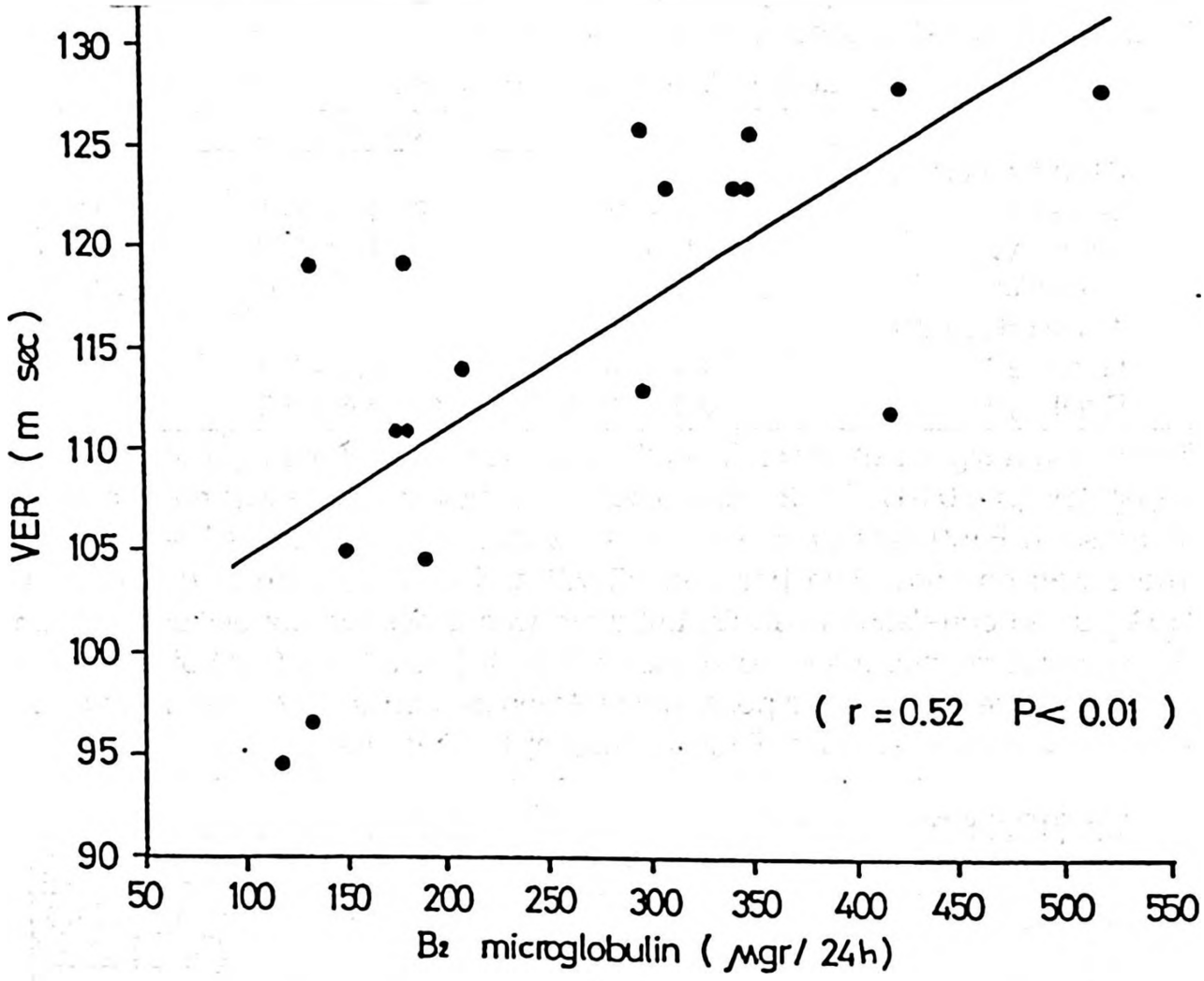

Fig. 3: Correlation between β_2-microglobulin in urine and P100 latencies of left eye in diabetic patients.

Table III: Nerve Conduction Velocities

	Diabetic Patients	Control Group	P
Motor NCV (m/sec)			
N.medianus	54.53 + 10.56	57.25 + 6.88	> 0.05
N.personeus	46.38 + 11.38	54.27 + 6.89	< 0.05
N.medianus sensorial Latans (msec)	2.30 + 0.38	2.73 + 0.83	< 0.05

Motor nerve conduction velocity of n.peroneus correlated positively with the duration of diabetes (Fig. 4) (r: 0.49, $p < 0.05$) and with β_2 microglobulin (r: 0.52, $p < 0.01$).

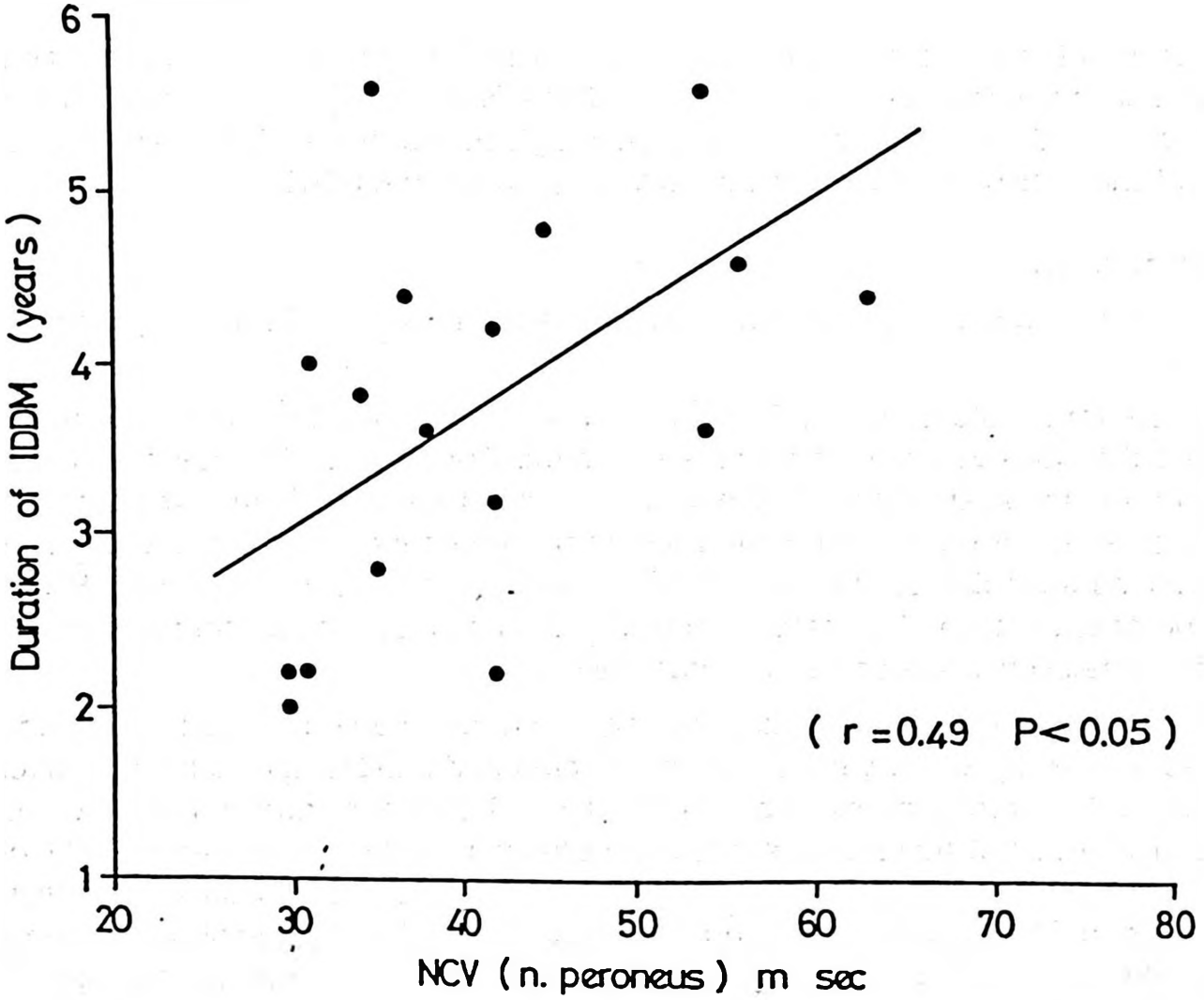

Fig. 4: Correlation between duration of diabetes and motor nerve conduction velocity of n.peroneus in diabetic patients.

Table IV: HbA_{1c} and β_2-microglobulin

	Diabetic Patients	Control Group	P
HbA_{1c} (g / dl)	11.8 + 2.4	5.42 + 0.80	< 0.001
β_2-microglobulin (µg / 24 hours)	311.28 + 56.78	89.96 + 20.35	< 0.001

The HbA_{1c} level of the diabetic patients was between 8.5 and 15 g / dl (mean 11.8 ± 2.4), and the HbA_{1c} level of the control group was between 4.5 and 6.9 g / dl (mean 5.42 ± 1.80). The difference between HbA_{1c} concentrations in diabetic patients and the control group was statistically significant ($p < 0.01$).

The β_2 microglobulin levels in the diabetic patients were between 196 and 711 µg / 24 hours (mean 311.28 ± 56.78), while the control group ranged from 72 to 135 µg / 24 hours (mean 89.96 ± 20.35). There was a significant difference between these two groups ($p < 0.01$).

Although there was no correlation between HbA_{1c} and motor nerve conduction velocities of n.medianus, n.peroneus and sensorial latency of n.medianus, there was a positive correlation between β_2 microglobulin and the NCV of n.peroneus and the sensorial latency of n.medianus (r: 0.52, $p < 0.01$).

Discussion

Our results demonstrate abnormalities in the PSVER and BAER of subjects with IDDM.

Since wave I latency of BAER was normal in our patients, it must be concluded that the observed abnormalities are central. Abnormal BAER has also been reported by other authors[1-6]. Whether these changes result from primary neural involvement or represent neural dysfunction secondary to vascular involvement remains speculative. Our study failed to show any correlation between BAER and age, duration of diabetes and HbA_{1c}. In one study[6] the authors also found no correlation between these parameters.

The mean latency of PSVERs of the right and left eye separately in our study group were significantly prolonged when compared with the age-matched control group. No correlation existed between PSVER and age, duration of diabetes and HbA_{1c}, but there was a positive correlation between the motor NCV of n.peroneus and P100 latency of the left eye. There was also a positive correlation between P100 latencies of both eyes separately and β_2 microglobulin. In most of the studies there was also prolongation of P100 latency in diabetic patients[7-10]. Our diabetic patients had no complaints related to the eye, their visual acuity was near normal and they showed no signs of retinopathy. Yet an appreciable delay of conduction in the optic nerve occurred in our patients. The delay was bilateral, suggesting that the visual pathway was diffusely affected. Since β_2 microglobulin is an indicator of control of diabetes, the increased amount of this indicator indicates poor control of diabetes, as in our study. Because of the correlation between β_2 microglobulin and P100 latencies of VER, we may say that the prolonged VER latencies were due to poor control of diabetes. Prolongation in the optic nerve parallels peripheral nerve conduction[10], which correlates with our study.

In our study NCV of n.peroneus correlated positively with the duration of diabetes, a finding confirmed by other studies[11].

Although NCV is associated with both the duration of diabetes and β_2 microglobulin, the III-V interpeak latency of both ears had a positive correlation with only β_2 microglobulin. β_2 microglobulin levels in our study group were significantly higher than those of the control group, but according to the literature[12] it is at the upper limit of normal values. Increased β_2 microglobulin

is the first sign of degeneration of renal tubular cells[13]. As β_2 microglobulin and latencies of BAER and VEP correlate positively, we may speculate that the degeneration of cells of the urinary and nervous system probably occur at the same time.

In our study the prolonged latencies of VER and BAER were detected in the absence of clinical abnormalities in the visual and hearing systems. Thus we can say that prolongation of latencies of VER and BAER are the first signs of CNS involvement in IDDM. These techniques are easy to perform and harmless to the patient. We recommend that these investigations be done in every diabetic patient, regardless of the duration of the disease.

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