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NEUROPHYSIOLOGICAL STUDIES OF PATIENTS WITH CLASSICAL PHENYLKETONURIA: EVALUATION OF RESULTS OF IQ SCORES, EEG AND EVOKED POTENTIALS*

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Neurophysiological studies were conducted in 42 patients with classical phenylketonuria. The results of the intelligence quotient scores, electroencephalogram, visual evoked potentials and brain-stem auditory evoked potentials were evaluated. When compared with the controls, the subjects demonstrated a significant prolongation in VEP P_1 and BAEP I-V interpeak latencies and an increase in VEP N_1P_1 amplitudes. No relationship was found between these pathological responses and metabolic control. However, the observation of normal intelligence quotient scores in 14 out of 18 patients who displayed a pathological prolongation in P_1 latencies led us to the conclusion that evoked potentials may have a significant role in the determination of neurophysiological defects and that even cases with good metabolic control may have some obscure neurophysiological dysfunction which should be evaluated more carefully. *Key words: phenylketonuria, intelligence quotient, electroencephalogram, evoked potentials.*

Classical phenylketonuria (PKU) is a metabolic disease which emerges as a result of a decrease or lack of phenylalanine hydroxylase enzyme activity. The disease leads to mental retardation, if not treated early[1]. It is a known fact that patients may mature to an intelligence level within normal limits if they are diagnosed early and started on a carefully controlled diet[2-4].

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Previous studies reveal that certain neurophysiological deficits, in particular learning, perception and perspective disabilities observed in patients with normal intelligence, indicate that minimal damage, undetected by the electroencephalogram (EEG) and intelligence quotient (IQ) tests, remain in spite of early diagnosis and treatment[5-7].

The pathogenesis of mental retardation in PKU is not clearly understood. Although certain theories have been advanced, the well known pathology is that it results from a disorder in myelinization[8-10].

Evoked potentials, defined as electrical responses of the central nervous system (CNS) to an external stimulant, are practical and sensitive tests used to observe the development of illnesses interrelated with myelin disorders[11-13].

In this study, we used evoked potentials along with the IQ test and EEG with the aim of determining the role and significance of evoked potentials in the diagnosis of neurophysiological disorders in patients with classical PKU.

Material and Methods

Forty-two patients with classical PKU, ranging in age from one to ten years were selected for this study. The patients were divided into three groups on the basis of the time of restricted diet initiation and the degree of metabolic control.

Patients who received therapy within a period of two months were classed as the "early treatment group", those with phenylalanine levels lower than 7.5 mg/dl on the average prior to the tests were classed as the "satisfactory metabolic control group", while the remaining patients were classed as the "poor metabolic control" group.

The first group consisted of nine patients who were treated early and whose metabolic control was satisfactory. The average phenylalanine level in this group was 5.80 mg/dl. The female/male ratio was 5/4 and mean age 1.91 ± 0.40 years.

The second group consisted of 23 patients who were treated early and whose metabolic control was poor. The average phenylalanine level was 11.96 mg/dl. The female/male ratio was 11/12 and mean age 3.98 ± 0.57 years.

The third group consisted of ten male patients who were treated late in the course of the disorder. The average phenylalanine level was 12.30 mg/dl, and mean age 5.80 ± 0.76 years.

The control group consisted of 23 patients. Since there was a wide range of age in these three groups, the second group and the controls were divided into two subgroups, namely groups a and b. Subgroup a consisted of patients over 3.5 years and subgroup b consisted of those under 3.5 years.

The IQ was measured, EEG was taken and visual evoked potentials (VEP) and

brain-stem auditory evoked potentials (BAEP) were studied in all patients. In 19 of the controls, the VEP and BAEP were studied and an EEG was taken while in four controls only the VEP and BAEP were studied. The evoked potentials were tested using Medelect ST.10 ER94A equipment.

VEP: The electrodes were positioned on the occipital area and on the forehead at a distance of 80 cm from the monitor and the TV checkerboard using 50' checks on a 30° visual angle screen. A stimulus was applied once or as multiples of 128 with two alterations per second. The potential values between 10-100 Hz wave lengths were recorded and the average responses were calculated. The eyes were tested separately. The first positive wave P_{100} was considered primary data in evaluating VEP waves and taken as "latency". The amplitude values of N_1P_1 components were held by calculating the distances between two extreme points.

BAEP: The electrodes were positioned over the mastoid and vertex and both ears were stimulated separately by applying 10 stimuli/sec alternating clicks at one and multiples of 1024 (150-3000 Hz interval). A sound of 75 dB intensity was produced and placed by the stimulated ear. In evaluating the results, I-V interpeak latency, which was the central transmission time, was used.

EEG: Routine traces which were recorded by the electrodes positioned according to the 10-20 international system, taken by 8 channel mono and bipolar connections were evaluated using Nihon-Kohden equipment.

Psychometric evaluations: Either the Bayley Intelligence Development Test, Stanford Binet or Wechsler tests were given to measure intelligence quotient scores.

Analysis of variance (ANOVA), one-way ANOVA, Student's *t* test and a correlation test were used for statistical analysis.

Results

VEP: Table I displays the mean values of P_1 latency of the patient and control groups and their statistical analyses.

Out of a total 42 patients, delay in P_1 latency was detected in at least one eye of 22 patients and a statistically significant difference was noted only between the values of the patients in group II and the control values (Fig. 1; $p<0.05$). The other groups and sub-groups did not display a statistically significant difference either with each other or with the control group.

Table II shows VEP N_1P_1 amplitude values and the results of statistical studies. No statistically significant differences were found in N_1P_1 values between the groups. Amplitudes over 20 μV which could be qualified as giant amplitudes were obtained in 15 out of a total 42 patients.

Table I: VEP P_1 Latency Values in the Patient Groups and in the Control Group

	Mean P_1 Latency Values (msec)				
	Left Eye		Right Eye		
Groups	$\bar{X}$	SD	$\bar{X}$	SD	p
I	118.64	8.25	120.13	8.70	I vs II n.s.
II	128.85	6.82	131.67	7.08	I vs III n.s.
III	118.42	9.13	121.98	8.62	I vs C n.s.
C	105.53	1.25	104.59	1.16	II vs C < 0.05
					III vs C n.s.
	F: 3.476		F: 4.56		

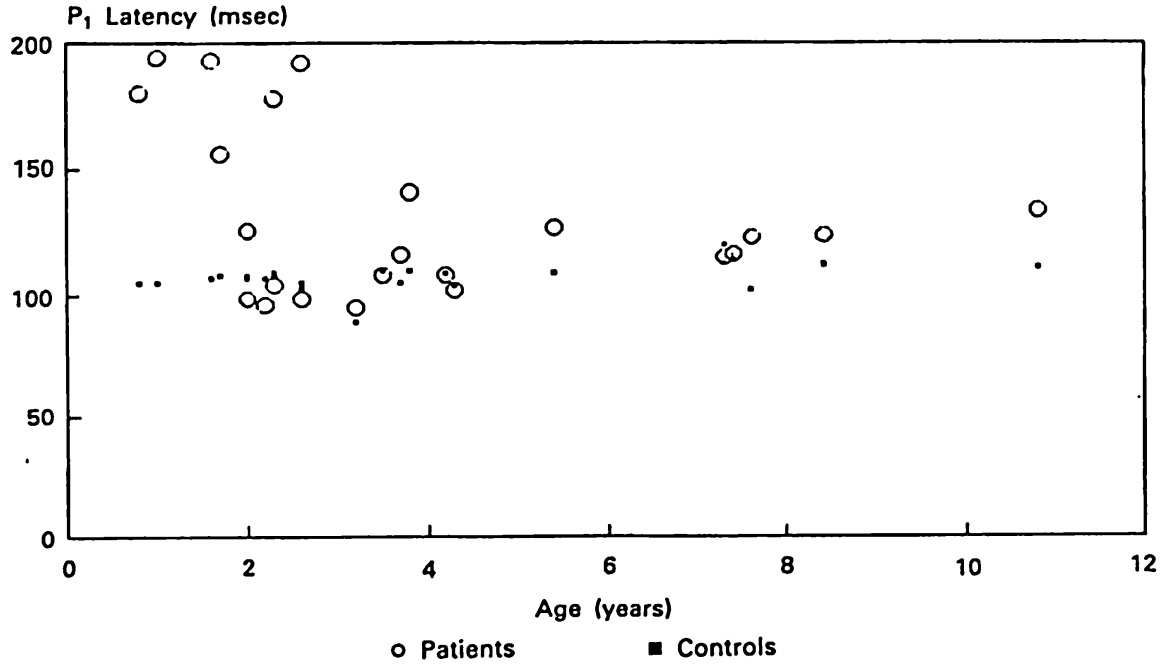

Fig. 1: VEP P_1 latencies according to age in group II and control group.

Table II: VEP N_1P_1 Values in the Patient Groups and in the Control Group

	Mean N_1P_1 Amplitude Values (μV)			
	Left Eye		Right Eye	
Groups	$\bar{X}$	SD	$\bar{X}$	SD
I	16.33	1.34	15.68	1.51
II	18.25	1.99	19.31	1.84
III	15.61	2.56	12.71	2.71
C	17.94	1.75	17.16	1.71
	F: 0.3107 n.s.		F: 1.6278 n.s.	

BAEP: Table III gives I-V interpeak latency values. Although a definite prolongation relative to the control group values was observed in all groups, a significant difference was noted only in the left ear between group I and the control group (Fig. 2; $p<0.05$). This result is due to the difference in the values of the control group.

Table III: BAEP I-V Interpeak Latency Values in the Patient Groups and in the Control Group

	Mean I-V Interpeak Latency Values (msec)					
	Right Ear			Left Ear		
Groups	$\bar{X}$	SD	p	$\bar{X}$	SD	p
I	4.27	0.13	n.s.	4.27	0.09	I vs II n.s.
II	4.07	0.07	n.s.	4.18	0.07	I vs III n.s.
III	4.14	0.06	n.s.	4.15	0.03	II vs III n.s.
C	3.99	0.04	n.s.	3.97	0.05	I vs C < 0.05
						II vs C n.s.
						III vs C n.s.
	F: 2.2278 $p > 0.05$			F: 3.0432 $p < 0.05$		

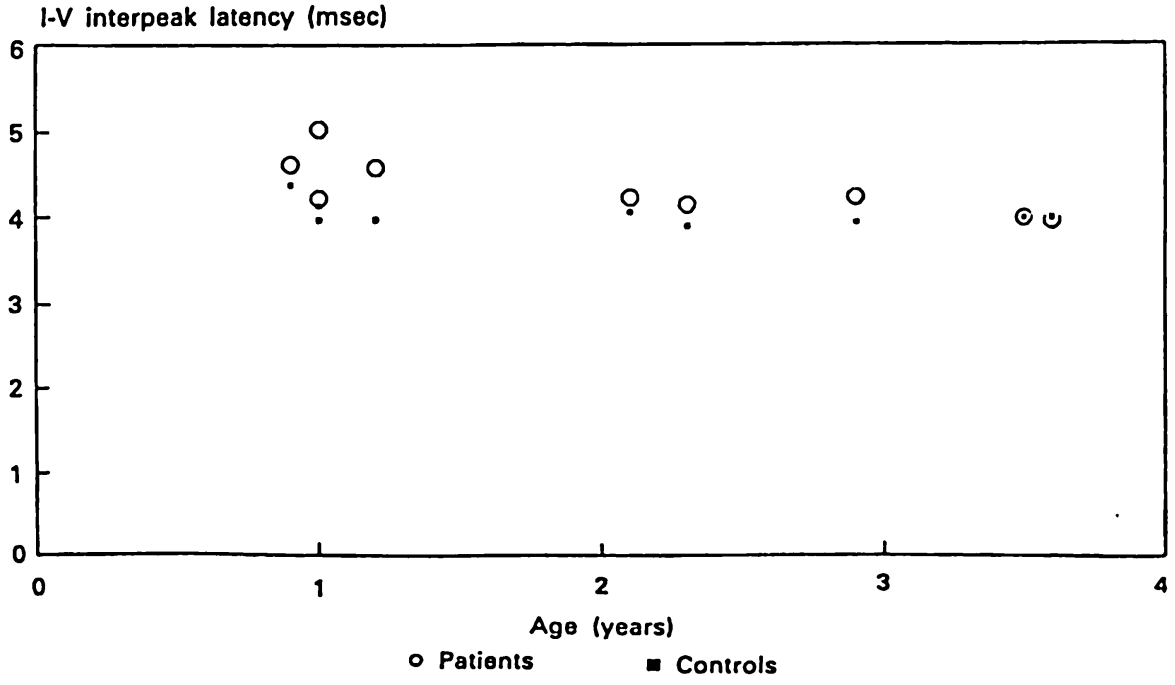

Fig. 2: BAEP I-V Interpeak latencies according to age in group I and control group.

EEG: The EEG traces were evaluated in terms of ground paroxysmal activity and asymmetry between the two hemispheres. The EEG was found to be pathologic in 17 out of 42 patients. Of the nine patients in group I, three had paroxysmal activity and one had paroxysmal activity with dysrhythmia (44%). Of the 23 patients in group II, seven had paroxysmal activity and one had paroxysism together with dysrhythmia (23%). Of the ten patients in group III, four had paroxysmal activity, one had paroxysism and dysrhythmia and one only had dysrhythmia (60%). Of the 19 controls in whom EEG tracings were taken, one had dysrhythmia and another had latent paroxysmal activity (10.5%). A statistically significant difference was found on the EEG between those who received late therapy and the control group. No relationship was found between convulsions and EEG disorders.

Psychometric evaluation: IQ and development scores were as follows: 102.11 ± 4.84 in group I (on early and rigid diet), 93.30 ± 4.08 in group II (poor metabolic control), and 28.90 ± 4.08 in the late therapy group. Four patients in group III could not be tested due to severe mental retardation. A statistically significant difference was found between groups I and III and groups II and III (Table IV).

Table IV: Mean IQ Values in Patient Groups

	Mean IQ Values and Development Scores		
Groups	$\bar{X}$	SD	p
I	102.11	4.84	I vs II n.s.
II	93.30	4.08	I vs III < 0.05
III	28.90	8.15	II vs III < 0.05

F: 41. 8887

When evaluated in terms of their IQs, all patients in group I, while only 60.9 percent of patients in group II were found to have an IQ within normal limits. These findings were statistically significant for all groups (Table V).

Statistical analyses were performed with regard to the IQ, VEP and BAEP results of the sub-groups delineated by age, but no significant difference was found. Negative correlation values were found for age and all other data, whereas a positive correlation coefficient of 0.001 was found between VEP P_1 latencies and BAEP I-V interpeak latencies.

Table V: Comparison of Psychometric Test Results in Terms of IQ

IQ Score	Group I		Group II		Group III	
	n	%	n	%	n	%
Mentally retarded (< 68)	–	0.00	2	8.70	10	100.00
Borderline (68-89)	–	0.00	7	30.40	–	0.00
Normal (> 90)	9	100.00	14	60.90	–	0.00
Total	9	100.00	23	100.00	10	100.00

for all groups $p < 0.05$

Discussion

Mental development in PKU is influenced by various factors, the two most important of which are early dietary treatment and optimal metabolic control. The results of previous studies indicate that patients who receive treatment within the first two months of life can attain an IQ within normal limits, while those with an average blood phenylalanine level below 7.5 mg/dl achieve maximum IQ capacity[14-18]. Nevertheless, in spite of a normal IQ, PKU patients are usually confronted with common problems such as learning disabilities, poor mathematical comprehension, changes in behaviour and a poor attention span[5,16,19,20]. IQ tests and EEG have been frequently used to diagnose patients with mental retardation and convulsions.

The use of evoked potentials which play an important role in the diagnosis and monitoring of patients, in particular those with a myelinization disorder dates back to the early 1980s. A limited number of such studies of PKU patients are reported in the literature. Hecox et al[21] was first to report that the BAEP I-V interval was longer in a two-year-old untreated patient than in treated patients. Creel and Buehler[22] reported a definite prolongation in P_1 latencies of VEP applied to untreated adult patients. Recent studies have investigated the relationship between evoked potential responses and metabolic control. Giovannini et al[23] could not find a significant difference between the patients and controls in a 14-case series, but which when evaluated in terms of metabolic control, they observed that P_1 values were significantly lower in the group with good metabolic control.

Meanwhile, in a study of 41 adolescents with hyperphenylalaninemia, Korinthenberg et al[24] showed that there was a definite prolongation in P_1 latencies and a variation in BAEP responses between patients and controls, but no correlation was reported between continuation of the diet therapy, phenylalanine concentrations, EEG or IQ test results. They claimed that the prolongation in the latencies is an indicator of demyelinization in PKU. The existence of a strong positive correlation between P_1 latency and BAEP I-V interpeak latency and the prolongation in latencies lead us to believe that there is extensive dismyelinization in PKU. Another observation which we have not come across in previous studies is the increase in VEP N_1P_1 amplitudes of the patients. Although not statistically significant, this observation is interpreted as being a possible indicator of increased hyperexcitability in PKU patients. Some studies have shown that the transmitter changes lead to giant amplitudes by disturbing synaptic transmission[25]. There are also studies reporting that toxic metabolites inhibit transmitter synthesis[9]. This hyperexcitability might explain the EEG pathologies and convulsions observed in patients with PKU.

As for the VEP and BAEP values in our study, no significant results were obtained for any of the groups when the sub-groups established on the basis of homogenous age distribution were compared with each other. This finding can be interpreted in two ways: 1) The increase in the number of subjects due to disaggregation into sub-groups, 2) Evoked potential responses display pathology independent of metabolic control. Pathological responses also in patients with good metabolic control can be accepted as proof of the fact that the brain can not totally be protected even in cases where normal IQ scores are attained through early therapy and rigid diet. In this respect, it is clear that evoked potentials may play an important role where IQ tests are inefficient in monitoring patients with PKU, in particular those having normal IQ scores.

Different results in various studies, though limited in number, support the second explanation[22-24]. Another fact which supports this explanation is that a pathological response was obtained in only four of our patients who were mentally retarded and diagnosed late.

The most significant and interesting finding in our study was that the IQ scores were within normal limits in all but four of the 18 patients in groups I and II having prolongation in P_1 latencies. The prolongation in P_1 latencies in a PKU patient with a normal EEG and IQ score should be interpreted as an indicator of pathologic myelinization.

This was a preliminary study, which for more concrete interpretations, should be supported by similar studies carried out in a larger series of age-matched patients and controls.

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