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Original Paper

Hearing in Children with Phenylketonuria

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ABSTRACT

Background: Phenylalanine is an essential Acid Amine participates in protein synthesis by tyrosine. High levels of phenylalanine in the body lead to the production of large quantities of phenyl ketone, which is excreted through urine and that is why it called as Phenylketonuria. A defect of IQ and attention, visual ability and speech processing in this patient. the aim of this study was hearing threshold evaluation of this patient. **Method:** In a cross-sectional, descriptive study auditory brain stem responses and otoacoustic emission of patients from 1 to13 years and control group age range of 1 to 14 years evaluated. **Results:** In 31 patients (62%) delay in ABR waves were outside of the normal range but the overall mean of all waves had in the normal range and the average interval of waves in patients with delay in treatment delay was more than patients group with early treatment. **Conclusion:** delayed-treatment was faced with more delays in the intervals between ABR waves, although statistically was not significant.

BACK GROUND

Phenylalanine is an essential Acid Amine participates in protein synthesis by tyrosine. Phenylalanine hydroxylase enzyme defect or its cofactor called BH4 leads to the accumulation of phenylalanine in the brain and body fluids. High levels of phenylalanine in the body lead to the production of large quantities of phenyl ketone, which is excreted through urine and that is why it called as Phenylketonuria. The most common organ central nervous involved in the system. Children are normal at birth, but if be not timely diagnosed and treated, are struck with mental retardation and severe cognitive disorders (1). Another finding of these patients is the existence of IQ deficits, attention, abstract thinking, neurotransmitter disturbances and construction defects in sub-cortical white matter and frontal lobe (2 and 3, 4, 5). Electrophysiological studies that use the auditory evoked potentials are one of the objective methods to evaluating the function of auditory (6). So measuring this potential of the hearing can be revealed functional changes in that auditory pathway occur from the cochlea and auditory nerve to the auditory cortex (7). It is important to know that untreated leads to different degrees of irreversible mental retardation, despite appropriate treatment can still remain problems with executive function (5, 8, 12, 9, 10 and 11). Also defects of IQ and attention, visual ability and speech processing in this patient may be occurred with initiation of treatment (14, 15, 13) Korinthenberg et al by evaluating brainstem auditory responses in 41 adolescents with a variety of HPA showed there is statistical difference between the intervals of waves I, III and III to V (16) in all patients during the first year of life are created Phenylketonuria And in terms of shape of the waves, there is no difference between patients group and control group (17). Ludolph performed a clinical and electrophysiological study and concluded that all patients that treatment had been begun for them during the first months of life have waves and intervals between waves in the normal range (18). Leuzzi showed that the shape of waves, absolute intervals of waves I, III, V and between wave intervals I to III, III to V and I to V, all were in the normal range (19) Ludolph concluded that patients with phenylketonuria can have changes in central auditory pathway have been not still specified a significant correlation between brain auditory changes and diet control significantly. (20) Patrícia Cotta Mancini reported that although ABR observed differences are still low in terms of clinical diagnosis standards but also indicates that patients with PKU, will be with problems even if were diagnosed and treated early for them in their brain auditory pathways especially in pons (21).

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Launch the monitoring Center for patients with Phenylketonuria at Children's Hospital of Tabriz, that is a referral center for children of North West of the country became an incentive to attempt to investigate auditory disorders in these children in Iran for the first time.

MATERIALS AND METHODS

In a cross-sectional, descriptive study that we conducted at the Center of Research and Clinic of monitoring patients with Phenylketonuria located at Children's Hospital affiliated to Tabriz University of Medical Sciences and Health Services.

With regard to the power of 80% in this study Zb = 0.84 was considered. Also taking into consideration the significance level of 0.05 was considered Za = 1.96. Also in this formula value of r = 1 was considered due to equality of number of people in case and control groups. By taking the average of 25% for impairment in Case group and 5% in the control group, according to previous studies, the sample size was calculated at least 49 patients in each group. In this study, 50 patients with Phenylketonuria that their disease in terms of clinical and laboratory criteria had already been proven and at the center of Phenylketonuria disease of Children's Hospital of Tabriz had records outpatient follow-up and periodically in order to continue his treatment were referred to the clinic and 50 children with fractures special for the nose for relocation of fracture under anesthesia in the surgery room were hospitalized in section of ENT, during the referral to the clinic randomly and tandem were selected after ensuring the absence of withdrawal from the study for each patient.

Having phenylketonuria disease and clinic file at Children's Hospital of Tabriz is inclusion criteria for patients and exclusion criteria for both groups included children with syndromes, congenital abnormalities of the outer ear, children with any underlying systemic disease, such as hypothyroidism, diabetes, consent for the patient to participate in the study, a history of resuscitation, mechanical ventilation, blood transfusions and birth weight below 1500 grams. The patients initially were otoscopic examined by a doctor who specializes in ear, nose and then demographic, current age and the patient's age at diagnosis time, start time of treatment and serum level of phenylalanine in the diagnostics of serial serum level of phenylalanine During treatment and initiation time of treatment and type of treatment regimen and information about parent and. was recorded for patients with phenylketonuria and using audiometer includes evaluation of brain stem response to sound (Auditory brain stem response/ABR) and the inner ear Acoustic emission (Otoacoustic emissions/OAE) and factors influencing its changes were evaluated Auditory brainstem response (ABR) typically uses a click stimulus that generates a response from the hair cells of the cochlea, the signal travels along the auditory pathway from the cochlear nuclear complex to the inferior colliculus in mid brain generates wave I to wave V.

Wave I: small amplitude, delayed or absent may indicate cochlear lesion

Wave V: small amplitude, delayed or absent may indicate upper brainstem lesion

I – III inter-peak latency: prolongation may indicate lower brainstem lesion.

III – V inter-peak latency: prolongation may indicate upper brainstem lesion.

I – V inter-peak latency: prolongation may indicate whole brainstem lesion. Shortening of wave the interval with normal latency of wave V indicate cochlear involvement

Results of intervals between the waves I-III, III-V ABRs in the patient group compared to normal values confirms the relative delay although generally is in the normal range.

Data Analysis

IBM SPSS 21.0 Statistics was used for data analysis. This study employed descriptive statistics tests including mean, standard deviation, as well as frequency and percentage.

Ethical Considerations

Prior to using the data on the patient's records, informed consent was obtained from the patient's parents, and the study procedure was approved by the Ethics Committee of Tabriz University of Medical Sciences, on June 12, 2014, under No. 93/3/7/9.

Since the beginning of the treatment regimen before the start of 90 days of birth was considered as an early treatment. Independent statistical t-test was used to compare the ABR in two groups and Chi-square test and Fisher's exact test when necessary was used to compare OAE in the two groups.

The overall results with ABR obtained from the patients group in Tables 1 to 3 and Figures 1 and 2 have been drawn.

Based on the results obtained, the number of patients and the control individuals is equality and equivalent to 50 patients in each group.

Ranging in age of patients from 1 to13 years with an average age of 5.7 years and control group age range of 1 to 14 years with an average of 6.7 years.

RESULTS

In patients group 29 (58%) were males and 21 (42%) were female in the control group, 33 patients (66%) were males and 17 (34%) were female.

The average head circumference in the patients in the control group, was 34.6 and in control group was 34.9, that both range were normal and without significant difference statistically (P=0.155)

None of the group of patients and control has history of blood transfusions, connected to ventilator, resurrect history and audition disorders or genetic diseases or congen-

Table 1: Left and Right Ear OAE Test Results in Patient and Control Groups, in Percentage

Table 2		Right Ear		Left Ear	
Group	Results (%)	Refer	Pass	Refer	Pass
Patient		12	88	14	86
Control		4	96	4	96

Table 2: ABR Wave Intervals, Divided by Early and Delayed Treatment in the Right and Left Ears of Patients

Wave Interval	I-III				III-V				I-V			
Group	Delayed		Early		Delayed		Early		Delayed		Early	
Ear	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Max	2.91	2.83	2.73	2.71	2.52	2.48	2.37	2.35	5.31	5.15	4.77	4.85
Min	1.8	1.76	1.89	1.95	1.85	1.72	1.72	1.46	3.83	3.59	3.9	3.85
Mean	2.37	2.25	2.18	2.15	2.14	2	2.07	2.06	4.51	4.25	4.26	4.22

Table 3: Investigating the Frequency Distribution of Mental Retardation and Epilepsy in Patients with PKU

Table 1	Mental Retardation (%)	Epilepsy (%)
Total Patients – 50 Subjects	11 (22)	9 (18)
Delayed Treatment– 14 Subjects	7 (50)	5 (35.7)
Early Treatment – 36 Subjects	4 (11.1)	4 (11.1)
ABR Wave Latency – 31 Subjects	9 (29)	8 (25.8)

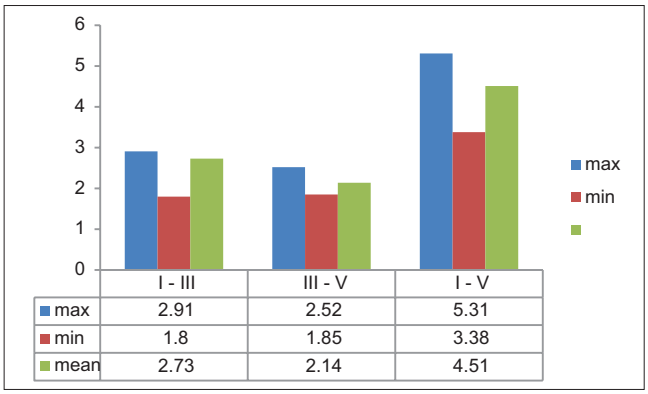

Figure 1: ABR of R.ear of patients

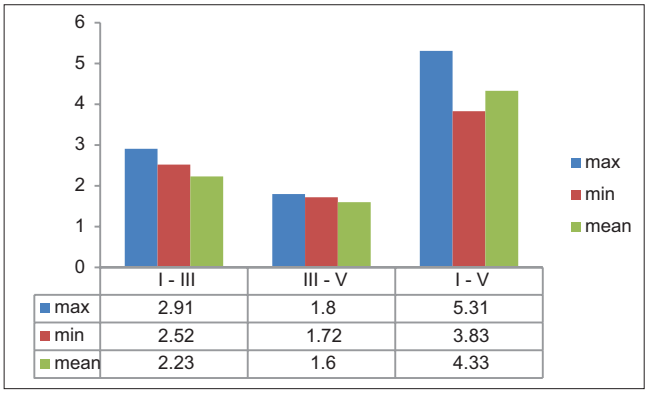

Figure 2: ABR of L.ear of patients

ital anomalies in their parents. A history of jaundice in the patient group 12 (24%) and in the control group, 15 (30%) patients was not statistically significant different (P=0.499). The number of patients that had begun with screening early treatment for them, 36 (72%) patients and late onset was in 14 (28%) patients that were related to the period of prior screening.

Serum levels of for patients with Phenylketonuria at diagnosis for an average was19.75 and with maximum of 48 and minimum of 4.3 mg per deciliter.

The average age of fathers in the group of patients 30.7 and in the control group was 29.3, and the average age of the the mothers in patient group was 27.5 and in the control group was 25.5, that there was no statistically significant difference between age of fathers (P=0.121), but the difference observed in mothers' age was significant (P=0.040).

Kinship of the parents in patients group in parents was 7 (14%) children and in control group in parents were 14 (28%) children. The highest relative was cousin (male) - cousin (female).

Education level of fathers in the group of patients in 80% (n = 40) of cases at the level of diploma or less and 6% (n=3) at the level of associate, 12% (n = 6) at the undergraduate level and 2% (n=1) were at the postgraduate level. Maternal education level of the patient group in 88% (n = 44) of cases at the level of diploma or less and 4% (n=2) at the level of associate, 6% (n=3) at the undergraduate level and 2% (n=1) were at the postgraduate level. Mental retardation in 11 patients (22%) patients with PKU was seen to different degrees and none of the control group was diagnosed with mental retardation.

An epileptic condition was seen in 9 (18%) of child with disease and the most common type was generalized tonic-colonic seizures. None of the control subjects were diagnosed with epilepsy. In two cases (4%) patients' right ear had otitis media and in the left ear of the patients was also seen two cases (4%), otitis media, and in the other two cases was seen (4%) due to the presence of a grommet type B. In 31 patients (62%) delay in ABR waves were outside of the normal range but the overall mean of all waves had in the normal range and the average interval of waves in patients with delay in treatment delay was more than patients group with early treatment.

DISCUSSION

Auditory brainstem response (ABR) shows the function of distal portion of the auditory pathway. This criterion specifies the sensitivity of the auditory pathway and helps to neuropathological diagnosis in the direction of the auditory nerve. A normal ABR has 5 to 7 waves and first 5 waves are considered in neurological diagnostic purposes. Waves of 1 and 2 show respectively auditory pathway in the distal and

proximal the cochlear nerve. Wave 3 shows the Core Activity Spiral and Wave 4 shows the superior olive complex activity. Wave 5 is related to activity in the lateral lemniscuses. Normal values in ABR are as distances between waves I-V<=4.4, III-V<=2.1, I-111<=2.3 is in milliseconds (22). According to literature review conducted, in most studies done on patients have been compared with phenylketonuria disease with control group in terms of auditory brainstem responses. (16, 17 and 18) but in our study, in addition to auditory brainstem response, tympanometry and acoustic emission in the inner ear were also studied. As well as the role of demographic factors and the possible connections between them were evaluated. In the present study ABR performed in children with PKU whether early treatment and delayed-onset treatment, on average was in the intervals between waves of I to III and III to V and I to V and the waveforms in both ears within natural range. But in comparison position with normal values, delayed-treatment group, were faced with more delays in the intervals between waves, although statistically was not significant. (P>0.05)

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