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Evaluation of Developmental and Hearing Disorders in Phenylketonuric Patients

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KEYWORDS

Phenylketoneuria, Hearing loss, ABR.

A B S T R A C T

Phenylketoneuria (PKU) is a metabolic disease caused by a mutation in the gene that codes the phenylalanine hydroxylase enzyme, which is responsible for transforming the amino acid phenylalanine into tyrosine. Elevated levels of phenylalanine in the blood results in a toxic effect with mental retardation being the most significant manifestation of this disease. The aim of this study is to evaluate the audiometry and auditory brainstem responses (ABRs) to determine the effects of treatment on the neurologic evolution of the auditory pathway in patients with PKU. In a descriptive cross-sectional study, a group consisting of 50 children with PKU was compared with 50 healthy children, in terms of the Audiometry, ABRs and their affecting factors. In this study, results of ABRs in the patient group compared to normal values confirms the relative delay (though generally in the normal range) in the intervals between the waves I-III, III-V and I-V and developmental delays and mental retardation and seizures were more prevalent in Phenylketoneuria patients. The results of this study showed that verbal and developmental disorders may be affected by undiagnosed hearing loss, thus, we recommend that all infants, especially Phenylketoneuria patients should be evaluate for hearing and speech disorders.

Introduction

Phenylketoneuria (PKU) is a metabolic disease that is genetically transmitted in an autosomal recessive form, caused by a mutation in the gene that codes the phenylalanine hydroxylase enzyme, which is responsible for transforming the amino acid

phenylalanine into tyrosine (1). Elevated levels of phenylalanine in the blood facilitates the passage of this enzyme in excessive amounts into the central nervous system, where its accumulation results in a toxic effect with mental retardation being the most significant manifestation of this disease(2). Treatment consists of dietary restriction of phenylalanine (3). Nonetheless, cases of executive function deficits are reported in patients with phenylketonuria, even at the early stages of continuous treatment (4).

Electrophysiological examinations using auditory evoked potentials are considered as an objective method for auditory function testing (5).

The present study was aimed at investigating the Developmental and Hearing disorders in patients with Phenylketoneuria.

Materials and Methods

In a cross-sectional descriptive study taking place in the Research Center and Monitoring Clinic for Phenylketoneuria Patients, at the Children's Hospital, affiliated to Tabriz University of Medical Sciences, from August 2014 to October 2015, a group of 50 children with Phenylketoneuria, already diagnosed in terms of clinical and laboratorial criteria, who referred periodically to the clinic for follow-up after treatment, were selected, as well as, another group of 50 healthy children. Subsequent to ensuring the absence of exclusion criteria, the participants first underwent otoscopic examination by an otolaryngologist. Then, the developmental disorders such as delay in sitting, walking, talking, etc were evaluated and demographic data for both groups, and the disease-related information of Phenylketoneuria patients were recorded through questionnaires. Subsequently, audiometry as well as auditory brain stem responses and the pertaining contributing factors were investigated.

Inclusion and Exclusion Criteria

The inclusion criterion was having documented Phenylketoneuria and clinical records at Tabriz Children's Hospital. The exclusion criteria for both groups were syndromic children, congenital abnormalities of the outer ear, and any underlying systemic disease such as hypothyroidism and diabetes, dissent of the patient's parents from participating in the study, history of resuscitation, connection to the ventilator, blood transfusion, and birth weight below 1500 grams.

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. Comparison of the two groups was carried out using independent T test, chi squared, and Fisher's exact test, where necessary.

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.

Results and Discussion

The number of patients and control subjects were equally 50 to each group. The age of patients ranged from 1 to 13 years, at an average age range of 5.7 years, and the age

of control subjects ranged from 1 to 14, at an average of 6.7 years. In the patient group, 29 subjects (%58) were boys and 21 (%42) were girls, and as for the control group, 33 subjects (%66) were boys and 17 (%34) were girls. Head circumference average was 34.6 cm in the patient group and 34.9 cm in the control group, both of which were normal, indicative of no significant difference (P = 0.155). Infant jaundice was observed in 12 subjects in the patient group (%24), and 15 subjects of the control group (%30), which was not significantly different (P = 0.499).

Varying degrees of mental retardation was observed in 11 patients with PKU (%22), while, none of the control group subjects had mental retardation. (Table 1)

Two patients (%4) had conductive hearing loss in the right ear; two patients (%4) had conductive hearing loss in the left ear. The frequencies of ABR wave latency are shown in Chart 1.

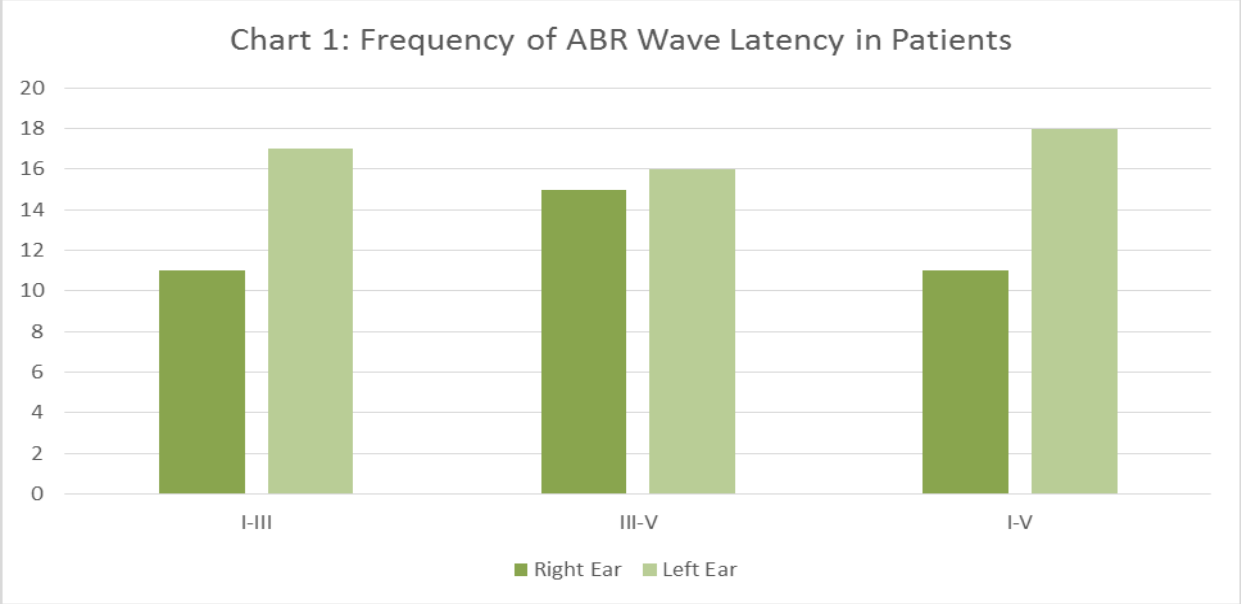
Investigating the literature revealed that most studies have compared ABRs of patients with PKU and that of the control group (6, 7, and 8). Cardona and colleagues in 1991 examined and compared 8 children with PKU and 58 healthy children in terms of ABRs in the first year of their lives. They concluded that the ABR criteria showed no considerable differences in waveforms I, III, and V, nevertheless, despite treatment, the interwave values of I through V was relatively higher in children with PKU than those of the control group (7). In their study in Brazil, in 2013, Patricia and colleagues compared a group of 25 patients with PKU to another group of 35 control subjects, in terms of ABR. The patient group was, per se, divided into two subgroups of early treatment and delayed treatment, consisting of 8 and 16 participants, respectively. According to their results, in the ABR of all patients, the I-V interval was higher compared to that of the control group; especially, in the delayed treatment group, mean interval of waves III and V and values of interaural wave V had increased. It was eventually concluded that although the discerned differences were not yet significant concerning clinical diagnostic standards, they still indicate the fact that despite early diagnosis and treatment, patients with PKU will experience complications in their brain auditory pathway, especially in the pons. In the end, the authors suggested that the patients with PKU should follow-up through electrophysiological auditory tests for detection and investigation of the mentioned complications (8). In addition to the larger sample size of the present study, compared to other studies, due to lack of epidemiological studies and a proper database on the hearing of PKU patients, besides ABR and tympanometery were simultaneously examined in the patients. The aim was to reveal complementary audiological examinations capable of determining the prevalence of auditory impairments in children with PKU.

According to our results, the average ABR in patients with PKU both in the interwave intervals I-III, III-V, and I-V, and the waveforms, in both ears, were within the normal range (P > 0.05).

The study by Siamak Shiva and colleagues in 2011 on 50 patients with PKU reported the frequency of seizures in these patients at 34%. Out of the patients with seizures, 88.2% had abnormal electroencephalograms, and the most common seizures were generalized tonic-clonic seizures and infantile spasms (9).

Table.1 The frequency of developmental delay in children with the PKU.

Case	Percent
Mental retardation	22
Delay in sitting	26
Reduction in head circumference growth	18
Convulsion	18
Delays in walking	12
Delays in speech	28



In our study, similarly, generalized tonic-clonic seizures were the most common (77.7%), however, the prevalence of seizures in our patients was estimated to be lower, at 18%.

In conclusion, with regard to our results we conclude that verbal and developmental disorders in patients may be due of undiagnosed hearing loss, thus, we recommend that all infants, specially phenylketonuric patients should be evaluate for hearing and speech disorders.

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