RESEARCH ARTICLE

PREVALENCE OF SEIZURE IN PKU: AN ANALYTIC HISTORICAL STUDY

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Abstract

Objective

Phenylketonuria (PKU) is an autosomal recessive metabolic genetic disorder characterized by a deficiency in the hepatic enzyme phenylalanine hydroxylase (PAH) which can cause problems with brain development, leading to progressive mental retardation, brain damage, and seizures. In this study we evaluated the frequency of seizure, EEG abnormality and behavioral disorders.

Materials & Methods

In this case study, 94 PKU children aged between 1 month and 23 years who were referred to Mofid children Hospital between 2009 and 2010 were enrolled. Patients were age and sex matched. Statistical tests were used for comparing patients' data.

Results

The mean age of patients was 8.4 years. Parents were relatives in 80.9% of the cases (76 patients). Of all, 43% (45 patients) had seizure but EEG was abnormal only in 81% of them (35 patients out of 43 patients). Totally, EEG was abnormal in 67% of the cases (63 patients) of whom 44.4% (28 patients of 63 patients) did not have seizure. Therefore, there was a significant relationship between seizure and EEG abnormality. The phenylalanine level ranged from 8mg/dL to 50mg/dL (mean: 18.88 mg/dL) at the time of diagnosis and from 0.4mg/dL to 18mg/dL (mean: 7.37mg/dL) at the time of evaluation. On the other hand, we observed abnormal behaviors in all EEG abnormalities and there was a significant relationship between EEG abnormality and behavioral disorders.

Conclusion

In our study, the prevalence of seizure was less than EEG abnormality and there was a significant relationship between EEG abnormalities and behavioral disorders in patients with Phenylketonuria regardless of seizure.The authors believe that treatment of EEG abnormalities may lead to the correction of behavioral disorders in these patients.

Keywords: Phenylketonuria, Seizure, EEG abnormality, behavioral disorder

Introduction

Phenylketonuria (PKU) is an autosomal recessive metabolic genetic disorder characterized by a deficiency in the hepatic enzyme phenylalanine hydroxylase (PAH) (1). This enzyme is necessary to metabolize the amino acid phenylalanine ('Phe') to the amino acid tyrosine. When PAH is deficient, phenylalanine accumulates and is converted into phenylpyruvate (also known as phenylketone), which is detected

in the urine (2). PKU (OMIM 261600) and its milder variant HPA are genetic disorders characterized by a deficiency in PAH (EC 1.14.16.1), an enzyme that is required to metabolize l-Phe to l-Tyrosine (l-Tyr). On the basis of blood Phe concentrations, PAH deficiency can be classified into classic PKU (Phe >1200 μmol/L), mild PKU (Phe = 600 1200 μmol/L) and mild HPA, where blood Phe is elevated above upper reference limit, but below 600 μmol/L (3).

The decreased PAH activity found in most forms of PKU and HPA are caused by mutations in the *PAH* gene, resulting in a non-functional PAH enzyme. Untreated PKU is associated with an abnormal phenotype including growth failure, microcephaly, seizures and intellectual impairment caused by the accumulation of toxic by-products of Phe metabolism. The incidence of PKU or HPA is highest amongst Caucasians, occurring in approximately 1 in 10,000 births. PKU can be detected in newborn screening tests as performed in most Western countries (4). Moreover, decreased or absent PAH activity can lead to the deficiency of Tyr and its downstream products, including melanin, l-thyroxine and the catecholamine neurotransmitters (5).

Serum phenylalanine concentrations in infants with PKU are normal at birth but begin to rise within the first few weeks of life. Excessive phenylalanine is generally thought to be responsible for the brain damage that underlies the severe mental retardation and seizure disorder of PKU. In untreated infants, cognitive delay becomes evident within 6 months and is progressive. The majority of affected children are unable to talk, and a significant proportion never learn to walk. Characteristic physical findings include light-colored hair and eye, skin pigmentation, an eczematous rash, hyperactive behavior and a musty or mousy odor (due to phenylacetic acid in the sweat).

Approximately 25% of the patients have generalized or partial seizures. Infantile spasms and myoclonic seizures may occur. On EEG, all patients have slowing epileptiform discharges or hypsarrhythmic patterns (6). The foundation of PKU treatment is a low Phe diet which, by reducing or normalizing Phe concentrations, prevents the development of the neurological and psychological changes. Since neurological changes have been demonstrated within one month of birth, it is recommended that dietary restriction should be started early and be continued through childhood when neural development is maximal (7). Clinical neurological abnormalities, affected neuropsychological performance and brain imaging in adults with PKU has led to a consensus that the PKU diet should be followed for life (8, 9).

Magnetic Resonance Imaging (MRI) shows white matter lesions in the brain of adult PKU patients and their size and number directly correlate with blood Phe concentration (10). Such changes can be reversed by lowering blood Phe levels (11,12). Accordingly, Phe treatment targets have been established (birth to 8 years: Phe 100–350 μmol/L, older children and adults: Phe <700 μmol/L). (13,14)

Materials & Methods

In this case study, conducted between 2009 and 2010, 94 PKU patients (45 male, 49 female) with a mean age of 8.49±6.24 years who were referred to Mofid Children Hospital, Tehran, were evaluated.

These patients were diagnosed either by newborn screening tests or later in life and were followed at Mofid Children Hospital. The diagnosis of PKU was made if serum phenylalanine concentration was above 6 mg/dl in untreated newborns (15). The patients were sex and age matched.

we reviewed of all medical records and past history of patients to revealed seizures. 94 PKU patients (45males, 49 females) constituted the study subject in this report. The age at onset of PKU ranged vastly from 1 month to 23 years. The diagnosis of PKU was made on the basis of serum phenylalanine (PHE) level more than 1200 mmol/L, clinical manifestations and urine Pterin analysis excluding atypical PKU. An informed written consent was obtained from parents or legal guardians. Age, sex and family history findings were recorded for all cases. A pediatric neurologist took the history of seizure in all cases and recorded positive findings, so all patients who recently had seizures were excluded. Blood samples were collected from all participants for the measurement of serum phenylalanine. All patients were referred for EEG recording after sleep deprivation for 8-12 hours.

DSMA IV was used to detect behavioral disturbances in all cases. Finally, statistical tests were applied for

comparing data patients' data and a P value less than 0.05 was considered significant.

Results

We studied 94 children (45 male, 49 female), with PKU. The mean age of the patients was 8.49 ± 6.24 years. Parents were relatives in 80.9% of the cases (76 patients). Of all, 43% (45 patients) had seizures and 47% (51 patients) were seizure free. Of cases with seizure, 20 (46%) were male and 23 (54%) were female (Table 1).

In patients with clinical seizure, EEG was abnormal in 81% (35 patients out of 43 patients with seizure) and normal in 19% (8 patients out of 43 patients with seizure); so, there was a significant relationship between clinical seizure and EEG abnormality (P<0.001) (Table 2).

EEG was abnormal in 67% of the cases (63 patients) while the remaining 31 patients (37%) had a normal EEG. In patients with an abnormal EEG, 44.4% (28 patients out of 63 patients) had no clinical seizure.

In patients with EEG abnormality, 34 (53%) had mild, 9 (14%) had moderate and 20 (33%) had severe abnormalities. Fifteen patients (44%) with a mild EEG abnormality and 12 patients (60%) with a severe EEG abnormality had clinical seizures. We found a significant relationship between clinical seizures and the severity of EEG abnormalities (P<0.001) (Table 3).

The frequency of behavioral disturbances was 73 (77.7%) in our patients and there was a significant relationship between behavioral disturbances and EEG abnormality (P<0.001).

Phenylalanine level ranged between 8 mg/dL and 50 mg/dL (mean: 18.88 mg/dL ±7.76) at the time of diagnosis and between 0.4 mg/dL and 18 mg/dL (mean: 7.37mg/dL ± 4.84) at the time of evaluation.

There was no significant relationship between clinical seizure and phenylalanine level.

Table 1. The prevalence of seizure according to the gender of the patients

		SEIZURE		Total
		negative	positive	
SEX	female	26	23	49
	male	25	20	45
Total		51	43	94

Table 2. Correlation between EEG and seizure in patients

		SEIZURE		Total
		negative	positive	
EEG	ABNORMAL	28	35	63
	NORMAL	23	8	31
Total		51	43	94

Table 3. The relationship between the pattern of EEG changes and seizure in patients

		SEIZURE		Total
		negative	positive	
EEG	Mild	19	15	34
	Moderate	1	8	9
	severe	8	12	20
	Normal	23	8	31
Total		51	43	94

Discussion

Several neurodegenerative disorders cause seizure, including the following: Alzheimer's disease, Creutzfeld-Jakob disease, Neurofibromatosis, Phenylketonuria (PKU), Tuberous Sclerosis, Sturge-Weber syndrome, Tay-Sachs disease, etc (16).

Metabolic diseases of the nervous system vary considerably in their clinical and pathological aspects. In these disorders, mental retardation and epileptic syndrome are the prominent presentation.

Pulariani studied 27 patients aged between 3 months and 3 years: 15 PKU cases, 4 homocystinuria cases, 1 hyper-prolinemia patient, 5 methylmalonic academia cases and 2 cases of combined disorders. He found epileptic syndrome in 21 patients, mental retardation in 1, spasticity in 5 and ataxia in 1 patient. Epileptic syndrome manifested with generalized seizures (grand mal: 6 cases, myoclonic absences: 13 cases) and partial seizures (simple motor: 2 cases).

Investigations did not show a reliable correlation between certain forms of enzyme deficiency and EEG patterns. The best outcome was observed in the cases of PKU with early diagnosis (17).

Heike Rolle-Daya et al reported the electroence phalographic findings of 90 patients with phenyl-ketonuria (PKU) who were visited in one clinic.

Seventy three percent of the patients with classical PKU who were diagnosed and treated early (group 1) had normal EEGs, 23% had mild background abnormalities, and 4% had paroxysmal discharges. Only 31% of the patients in whom PKU was diagnosed after 6 months of age (group 2) had normal EEGs; however, 24% had background abnormalities and 45% had paroxysmal discharges (18).

To determine the importance of an abnormal EEG in phenylketonuria (PKU), Gross PT et al reviewed 137 EEGs from 48 patients with PKU. Patients were divided into three groups: group 1 (n = 14) had only normal EEGs, group 2 (n = 20) had only abnormal EEGs, and group 3 (n= 14) had normal EEGs in the beginning which became abnormal later (19).

In another study, the frequency of EEG changes was evaluated. This prevalence ranged from 50% to 73% in PKU patients.

We found EEG abnormalities in 63% that is similar to other studies.

Ghada M.H reviewed 60 cases with classic PKU of whom 21 cases (35%) had epilepsy. In that study, epilepsy was more prevalent in males than females (66.7% versus 33.3%) and 69.2% (27/39) of PKU patients who had no history of epilepsy in any stage of their life had normal EEGs (20). In our study, 43% of the patients had seizure and the prevalence of clinical seizure was 46% in males and 54% in females which was similar to the study by Ghada in which the prevalence was higher in males than females.

Ghada et al reported that about 25% of the children had seizure and more than 50% had electroencephalographic abnormalities (20). Also, in that study, the prevalence of seizure and EEG abnormality was 43% and 67% respectively which means that some patients had EEG abnormalities without any clinical seizures.

There is evidence that subclinical discharges can cause behavioral disorders and cognitive impairment. It seems that negative effects of these epileptiform discharges

on the choice reaction time, verbal and nonverbal skills and behavioral abilities lead to cognitive and behavioral disorder (21).

Smithet al used the Rutter Behavior Questionnaire for patients with PKU and school teachers assessed the frequency of common abnormal behaviors in 544 8-year-old children with phenylketonuria who were born in the United Kingdom. The diagnosis of PKU was made by routine testing in infancy. Patients had mannerisms, hyperactivity, signs of anxiety and were less responsive and more reclusive than controls. However, they were less aggressive and untruthful, more obedient, and not absent from school more frequently. The increased frequency of deviant behavior may be the result of both psychologic stress and neurologic impairment (22).

In our study, 76% of the patients had a pattern of behavior disturbance such as anxiety, hyperactivity and aggressiveness. These behavioral disorders were in accordance with their EEG abnormalities.

In conclusion, In our study, the prevalence of seizure was less than EEG abnormality. It means that some patients had EEG abnormalities without clinical seizure. Most patients who had seizure had abnormal EEGs, too. There was a significant correlation between EEG abnormalities and behavioral disorders in patients with Phenylketonuria regardless of seizure.

The authors believe that treatment of EEG abnormalities may lead to the correction of behavioral disorders in these patients.

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