Clinical and electrophysiological findings in patients with phenylketonuria and epilepsy: Reflex features

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Objective: Phenylketonuria (PKU) is the most common form of amino acid metabolism disorders with autosomal recessive inheritance. The brain damage can be prevented by early diagnosis and a phenylalanine-restricted diet. Untreated or late-treated patients may show mental retardation and other cognitive dysfunctions, as well as motor disability and/or epilepsy.

Methods: Three patients with PKU and epilepsy were recognized to have reflex epileptic features, and there were ten consecutive adult patients with PKU and epilepsy who were evaluated retrospectively. Medical history, ages at diagnosis and therapy onset, age at seizure onset, seizure types and reflex features, neurological findings, cranial imaging, electroencephalography (EEG) findings, and final clinical condition were evaluated. Reflex epilepsy features were examined in detail.

Results: The cases (6 females, 4 males) were diagnosed at ages between 3.5 months and 12 years. All patients had various degrees of mental–motor retardation and focal or generalized seizures with age at seizure onset varied between neonatal period and 15 years. Three patients had febrile seizure, 3 patients had myoclonia, and 3 patients had status epilepticus. All patients had abnormal EEG findings except one. There was a slowing of background activity, and generalized discharges were observed in 7 patients; 3 of them had asymmetrical discharges. One patient had right hippocampal sclerosis (HS), and another patient had hypointensities in the basal ganglia and corpus callosum. Reflex features were clinically observed in 3 of the patients; however, EEG results did not show any related findings. One patient had reflex seizures triggered by photic stimuli, hot water, and startling; one by photic stimuli; and the other one by startling.

Conclusion: Reports on the clinical and electrophysiological features of adult patients with PKU were scant. We emphasized that reflex clinical features may be observed in this metabolic disease, and focal epileptiform abnormalities and asymmetry may be present in electrophysiological evaluation besides the rare association with HS.

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1. Introduction

Phenylketonuria (PKU) is the most common disease among amino acid metabolism disorders with autosomal recessive inheritance. The overall incidence of the disease is about 1/4500-200,000. However, in countries with high consanguineous marriage rates, such as Turkey, the incidences are as high [1]. The most common form is deficiency of phenylalanine hydroxylase, the enzyme which converts phenylalanine (Phe) to tyrosine. The deficiency is due to a mutation in the phenylalanine hydroxylase gene located in chromosome 12q23.2. More than 500 mutations have been reported [2,3]. Early diagnosis is possible with neonatal screening test (Guthrie test).

Neurological manifestation includes mental retardation and other cognitive dysfunctions, as well as motor developmental disability and/or epilepsy [3–5]. Neurological changes begin to be observed in the first month of life when the neuronal development is the fastest. Tremor, para/hemiplegia, and psychiatric problems such as depression, anxiety, and phobia may be observed later in life in untreated or late-treated patients [1]. Early treatment can prevent permanent brain damage and neuropsychological complications [2,3]. Therefore, diagnosis and treatment at the earliest period is important.

Although neurological complications and electroencephalography (EEG) findings are well-known in the pediatric population, there are a limited number of adult case series and case reports [5–7]. Our aim was to investigate the clinical and EEG features of patients with PKU and seizures continuing in adulthood and to report 3 cases who show reflex features that have not been reported before.

2. Methods

In In Istanbul University, Istanbul Faculty of Medicine, Epilepsy Clinic, we retrospectively analyzed 10 patients with PKU and epilepsy...
who had been followed in our outpatient clinic for 2–18 years. All patients were invited to the hospital by phone. They were reevaluated in terms of medical history, ages at diagnosis and treatment onset, age at seizure onset, seizure types and reflex features, neurological findings, cranial imaging, EEG findings, and final clinical condition. All EEG findings were reevaluated and repeated with hyperventilation and photic stimulation, each applied twice. All patients had been diagnosed in the pediatric clinic, followed by the pediatric neurology clinic, and then transferred to the epilepsy clinic after reaching adulthood. All patients were informed and written consent was obtained.

3. Results

3.1. Demographic data and family history

Of the 10 patients with PKU, 6 were female and 4 were male with ages ranging between 19 and 36 years (Table 1). One of the patients (N: 1) who had a sister with PKU had a history of difficult delivery at home as well as exposure to drugs and radiation during antenatal period. Her sister did not have a history of seizure. Four patients (N: 2, 4, 7, 9) had second degree consanguinity, and the parents were cousins. One of them had a history of difficult delivery and epilepsy in the family. Two of them were siblings (N: 7, 9).

3.2. Age at PKU diagnosis and onset symptoms

The patients were diagnosed between the ages of 3.5 months and 12 years (Table 1). Eight patients presented to the hospital within the first months of life (3–6 months). Two patients were admitted with speech impairment at the age of 1 and 5 years; other patients presented with motor impairments such as inability to sit and hold the head up. Unfortunately, of the 8 patients presented to the hospital within the first few months of life, diagnosis was delayed by several months in 6 patients, 1 year in one patient, and 2.5 years in the remaining patient. Two other patients with speech delay were diagnosed after 6 and 11 years. Diagnosis was delayed because of a false negative heel prick test in one patient and false negative metabolic test results or not considering PKU in the differential diagnosis in the others.

Phenylketonuria (PKU) type was tetrahydrobiopterin deficiency in 3 of the patients (N: 2, 7, 9) and classic type in one of them (N: 3), whereas, this data could not be obtained for other patients.

3.3. Epilepsy features

Age at seizure onset varied between neonatal period and 15 years. Focal or generalized seizures were observed. Seven patients had been diagnosed with bilateral tonic–clonic seizures; 3 had myoclonus, 2 had nystagmoid jerks, 2 had focal motor seizures, and 1 had tonic–atonic seizures. One patient had absence seizures in the form of unresponsiveness and staring, and once had a generalized tonic–clonic seizure. Febrile seizures were observed in 3 patients, but the patient history did not reveal whether they were complicated or not. Status epilepticus was reported in 3 patients (N: 6, 7, and 8), twice in one at the ages of 19 and 20 years (Table 1).

3.3.1. Patients with reflex features

Reflex features were clinically observed in 3 patients.

1) The first patient (N: 1) was a 19-year-old female, diagnosed with PKU when she was 1.5 years old. She experienced her first seizure at the age of 15 years characterized by frequent vertical nystagmoid eye movement persisting for 5 to 6 h; bright, colored, and dynamic lights were reported to trigger the seizures; tram lights were extremely disturbing, and she could not go to shopping malls because of these complaints. Seizures were also provoked by somatosensory stimulation (during showers when hot water touched her head) and auditory stimulation (sudden voice). A feeling of pleasure was present during the seizures. Subsequently, she also suffered from focal to bilateral tonic–clonic seizures with head deviation to left and twitching in the left arm. She had febrile seizures when she was 2 years old.

2) The second patient (N: 6) was diagnosed with PKU at the age of 11 months when she presented with focal seizures 7–8 times a month, lasting 10–15 s. Seizures were characterized by head and eye deviation, sometimes accompanied by involuntary contractions in left or right arm and leg that evolved to bilateral tonic–clonic seizures. She had febrile seizures when she was 10 months old. The patient had been treated in intensive care unit twice because of status epilepticus at ages 19 and 20 years. During hospitalization, flexion posture in the arms triggered by sudden external stimuli, such as sound and touch, and low amplitude contractions lasting 2–3 min were observed.

3) The third patient (N: 8) was a 33-year-old male patient with a history of PKU for 21 years. His first seizure occurred at the age of 1 year while watching TV and consisted of a fixed stare towards the TV screen and twitching of the arms. He later developed seizures triggered by flashing lights and self-induced seizures elicited by waving his hand in front of his eyes when looking towards the sun. In addition to photosensitive seizures, he developed spontaneous generalized tonic–clonic seizures that occurred usually during sleep, with a frequency of 1 to 4 per month. Other than difficulty at birth, there was not any significant finding on his past medical records.

3.4. EEG findings

Electroencephalography findings were normal in 1 patient and showed diffuse slowing of the background in another patient (Table 1). The remaining 8 patients had epileptiform discharges along with slowing of background activity. Slowing of background activity was prominent on the anterior head regions in 2 patients and on the posterior regions in 1 patient. Generalized epileptiform discharges were observed in the rest of the 7 patients (N: 2, 3, 4, 6, 7, 9, 10). These discharges were asymmetrical and becoming prominent on the anterior regions in 1 patient and on the right hemisphere in 1 patient. One patient who had asymmetrical generalized epileptiform discharge on the right frontal region also had generalized discharges accompanying myoclonus (Fig. 1-2). One patient had generalized discharges during hyperventilation only (Fig. 3). Electroencephalography findings could not be triggered by appropriate stimuli in the laboratory in any of the patients reporting clinical clear-cut reflex features.

3.5. Neuroimaging of patients

Magnetic resonance imaging (MRI) examinations of 5 patients revealed increased white matter signal intensities on T2-weighted and Fluid-attenuated inversion recovery (FLAIR) images (Table 1). One patient showed lesions in the periventricular, occipital regions with cerebral and cerebellar atrophy. In 1 patient, white matter lesions and hypointensities in the corpus callosum and basal ganglia were detected. Interestingly, 1 of the patients showed right hippocampal sclerosis and bilateral periventricular white matter lesions. One patient had profound periventricular lesions and right temporal arachnoid cyst. The MRI images of 4 patients revealed no significant pathology (cisterna magna in one of them), and 1 patient did not have an MRI examination.

3.6. Final evaluation, antiepileptic treatment, and diet

Family members consistently reported that the prescribed dietary treatment had been instituted, but follow-up with sustained
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