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ARAŞTIRMA/RESEARCH

Neurological assessment of 38 late-diagnosed children with classic phenylketonuria

Geç tanı konulan 38 klasik fenilketonurili hastanın nörolojik açıdan değerlendirilmesi

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Abstract

Purpose: We investigated the neurological outcome of 38 late-diagnosed phenylketonuria patients with magnetic resonance imaging (MRI), electroencephalography (EEG), visual evoked potentials (VEP), intelligence quotients (IQ) and examined the correlation of these parameters with the age and the plasma phenylalanine levels of patients at diagnosis.

Material and Methods: Thirty-eight late-diagnosed classic phenylketonuria patients were enrolled in the study. Plasma phenylalanine levels were measured by spectrofluorometric method. MRI was evaluated by a pediatric neuroradiologist. Ankara developmental screening inventory (ADSI) and Wechsler intelligence scale for Turkish children (WISC-R) test were performed to detect IQ scores. Porteus Mazo test adapted for Turkish children intelligence test were performed to all children. The EEG of all patients were recorded. VEP was used to measure the electrical activity in the brain to visual stimulus.

Results: The high plasma phenylalanine levels and late-diagnosis were associated with low IQ scores, pathological EEG, and pathological VEP patterns. High PA levels were also associated with more serious white matter signal abnormalities.

Conclusion: Our results demonstrated the impact of early diagnosis and low levels of phenylalanine at diagnosis on the intellectual, neurological development and visual outcomes.

Key words: Late-diagnosed phenylketonuria, magnetic resonance imaging, visual evoked potential

Öz

Amaç: Geç tanı alan fenilketonuri hastalarında manyetik rezonans görüntüleme (MRG), elektroensefalografi (EEG), uyarılmış görsel potansiyeller (VEP) ve zeka katsayısı ile nörolojik açıdan etkilenme ve bu parametrelerin tanı yaşı ve kan fenilalanin düzeyi ile korelasyonu araştırıldı.

Gereç ve Yöntem: Çukurova Üniversitesi Tıp Fakültesi, Çocuk Metabolizma ve Beslenme Bilim Dalında başvuran geç tanı almış 38 klasik fenilketonurili hasta çalışmaya alındı. Kan fenilalanin düzeyleri spektroflorometrik yöntem ile ölçüldü. Ankara gelişim tarama envanteri (AGTE), Türk çocuklarına göre uyarlanmış Wechesler zeka testi (WISC-R) yaş gruplarına uygun olarak yapıldı. Tüm çocuklara Türk çocuklarına göre uyarlanmış Porteus Maze zeka testi uygulandı. Tüm çocuklara EEG kaydı yapıldı. Merkezi sinir sisteminin görsel uyaranlara verdiği yanıt VEP ile değerlendirildi. MRG ile santral sinir sistemi bulguları incelendi.

Bulgular: Yüksek plazma fenilalanin düzeyi ve geç tanı, düşük zeka katsayısı, patolojik EEG, patolojik VEP ile ilişkili bulundu. Yüksek fenilalanin düzeyi ciddi beyaz cevher sinyal değişiklikleri ile ilişkiliydi.

Sonuç: Çalışmamız erken tanının ve tanı anındaki düşük kan fenilalanin düzeyinin entellektüel , nörolojik gelişim ve görme üzerine olan etkisini göstermiştir.

Anahtar kelimeler: Geç tanı fenilketonuri, manyetik rezonans görüntüleme, görsel uyarılmış potansiyel;

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INTRODUCTION

Phenylketonuria (PKU; OMIM 261600) is a recessively inherited disorder of phenylalanine (PA) metabolism caused by a deficiency of hepatic apoenzyme phenylalanine hydroxylase. The overall incidence of the disease changes 5 to 350 cases per million births among different populations due to the geographical and ethnic variations. PKU is frequent in Turkey with an incidence of 1:4370-6000 due to consanguineous marriages at an average rate of 21.1%[1]. If untreated, PKU leads to marked neuropathological abnormalities resulting in profound mental retardation, microcephaly, epilepsy and behavior problems. The pathogenesis of brain dysfunction in phenylketonuria is still unknown[2,3] In the literature, emphasis has been on high brain phenylalanine as the pathological substrate that causes mental retardation.

Surtees and Blau[4] addressed the effects of blood phenylalanine on cerebral free amino acid concentrations, and the effect of high blood and brain phenylalanine on neurotransmitters, cerebral protein synthesis, and myelin metabolism. The clinical symptoms and signs of PKU almost exclusively concern brain dysfunction, although some untreated PKU patients with consequently high plasma phenylalanine concentrations escape from severe brain dysfunction.

Studies with magnetic resonance spectroscopy (MRS) by Weglage and et al[5,6] revealed that these patients have almost normal inteligence instead of very high phenylalanine concentration in brain. Chronic neurotoxicity causes changes in white matter of brain, which are visible by magnetic resonance imaging (MRI). There are reported studies with white matter changes in a large proportion of patients with PKU[7,8-10]. Also studies have shown significant reduction of amplitude and prolongation of latency of visual evoked potentials despite the absence of visual symptoms in children with late-diagnosed PKU[11,12]. PKU patients revealed a loss of 4 intelligence quotients (IQ) for each months of delay after birth until onset of treatmet[13]. Electroencephalography (EEG) abnormalities or epilepsy was established in one quarter of late-diagnosed PKU patients[14].

The aim of our study was to investigate the neurological outcome of late-diagnosed PKU patients with MRI, EEG, Visual evoked potential (VEP), IQ and examine the correlation of these parameters with the age of patients at diagnosis and the plasma PA levels at diagnosis.

MATERIAL AND METHODS

Thirty-eight late-diagnosed classic PKU patients admitted to Cukurova University Department of Pediatrics Division of Metabolism between 1990-2006 were enrolled in the study. Patients who had any factors other than PKU that could disturb the brain development were excluded from the study. Except four all the other patients were referred to our hospital for evaluation of mental-motor retardation.

Plasma PA levels were measured by spectrofluorometric method. All neuroradiological and neurophysiological studies was performed at diagnosis. The local ethics committee had approved the study and informed parental consent was obtained. Our study was in accordance with the principles of Helsinki Declaration. All 38 patients underwent cranial MRI with GE Vectra Scanner with spin-echo T1 and T2 weighted sequences in coronal, axial and sagital plan with a section thickness of 0.5mm. MRI were evaluated by a pediatric neuroradiologist. For patients aged 8-59 months Ankara developmental screening inventory (ADSI) intelligence test used and for older children Wechsler intelligence scale for Turkish children (WISC-R) test were performed. Also for all children Porteus Mazo test adapted for Turkish children intelligence test were performed.

The EEG of all patients were recorded using the international 10-20 system and 10-channel instrument. On demand hyperventilation and photic stimulation were done. All EEGs were evaluated according to background activity and paroxysmal patterns by a pediatric neurologist. Flash VEP were used for profoundly retarded and small children and pattern reversal VEP by 2 per second black and white checker were used for the other patients. Reference data for VEP peak latencies were obtained from 20 sex and age matched healthy children.

Statistical analysis

Statistical analysis was performed with a software program (SPSS 9.0 Windows-95). The Mann-Whitney U test was used for comparison of EEG,

VEP,MRG, IQ scores, plasma PA levels and age at diagnosis.

RESULTS

Among thirty-eight late-diagnosed classic PKU patients, 19 were male (50%), 19 were female (50%). Mean age were 29.8±29.6 months, range 7-120 months. The mean PA levels were 25.3±6.7 mg/dL range 17.28-37.62 mg/dL at diagnosis. 11 patients (28.9%) were diagnosed before age of one. In 27 patients diet treatment was started after one-year of age and in 11 patients diet treatment was started between 13-120 months of age. Thirty-four patients were born before PKU screening program available in Turkey and four PKU patients were detected after the routine screening program started. Second-degree consanguinity were observed in 23 patients (60.5%). Eight patients had siblings with PKU. Five (13.5%) patients were underweight, six patients (15.8%) were short and 21 patients were microcephalic at diagnosis. These growth parameters were never improved to appropriate levels for age and gender. 12 patients (31.5%) were profoundly (IQ<35), 14 patients (36.8%) were profound-moderately (IQ 36-50), 4 patients (10.5 %) were moderately (IQ 51-55), 7 patients (18.4 %) were mildly (IQ 56-68) retarded. One patient (2.6%) had near-normal IQ (IQ=80)(Table1).

Table1. The age, plasma levels of PA at diagnosis, abnormal , EEG findings and VEP findings in patients with late-diagnosed PKU patients.

Patient no	Age(months) at diagnosis	Plasma PA(mg/dl) at diagnosis	MRI-signal abnormalities	EEG	IQ	VEP
1	13	24.16	Bilateral fronto-temporal	Generalize slowing,mild background activity	30	Bilateral prolonged latency
2	15	19.18	normal	Generalize slowing,mild background activity	25	Bilateral prolonged latency
3	41	18.14	Bilateral parietal	normal	55	Bilateral low amplitude
4	37	17.76	normal	normal	41	normal
5	27	37.21	diffused	Subcortical epileptiform activity	20	Bilateral prolonged latency,low amplitude
6	12	17.28	Bilateral fronto-parieto-temporal	Cortical active epileptiform anomaly	43	Bilateral prolonged latency,low amplitude
7	11	21.43	normal	normal	42	normal
8	74	16.49	diffused	Bioelectric status	4	normal
9	18	17.70	diffused	Hypsaritmic pattern	25	normal
10	8	26.12	Bilateral occipito-parietal	Moderate background activity	48	normal
11	14	29.38	normal	Subcortical epileptiform activity	36	normal
12	18	36.13	normal	Subcortical epileptiform activity	20	normal
13	29	34.61	Bilateral occipito-parieto-frontal	normal	24	Bilateral prolonged latency,low amplitude
14	18	36.14	normal	Generalize slowing, subcortical epileptiform	38	Bilateral prolonged latency,

				activity		
15	8	22.45	Bilateral occipito-parietal	Bilateral cortical subcortical epileptiform activity	45	Bilateral prolonged latency
16	60	21.68	normal	normal	35	normal
17	4	29.66	normal	Moderate background activity,	55	normal
18	104	17.93	normal	Moderate background activity,	45	normal
19	96	17.34	normal	normal	39	normal
20	53	28.93	Posterior pons, bilateral cerebro-occipito-parietal	Cortical epileptiform activity	43	Bilateral prolonged latency, low amplitude
21	82	17.45	Bilateral fronto-parietal	normal	56	Bilateral prolonged latency,low amplitude
22	36	21.1	normal	normal	57	Bilateral prolonged latency
23	10	23.57	Left temporal lobe	normal	51	Bilateral prolonged latency
24	23	31.93	normal	normal	57	Bilateral low amplitude
25	15	26.73	Bilateral occipito-parieto-frontal	Moderate background activity, cortical subcortical epileptiform activity	43	Bilateral prolonged latency
26	16	20.42	Bilateral occipito-parietal	Mild background activity	56	Bilateral prolonged latency, low amplitude
27	13	30.38	normal	Bioelectric status	44	Bilateral low amplitude
28	4	24.31	Bilateral parietal	normal	65	Bilateral prolonged latency
29	9	23.96	Bilateral occipito-parietal,centrum semiovale	Mild background activity	60	Bilateral prolonged latency
30	15	34.61	Bilateral occipito-parieto-frontal	Moderate background activity, cortical subcortical epileptiform activity	55	Bilateral prolonged latency
31	6.5	17.63	Bilateral occipito-parieto-frontal	normal	33	Bilateral prolonged latency, low amplitude
32	8	22.68	normal	subcortical epileptiform activity	41	Bilateral prolonged latency, low amplitude
33	24	24.72	normal	normal	56	Bilateral prolonged latency, low amplitude
34	25	33.68	normal	subcortical	21	Bilateral prolonged

				epileptiform activity		latency, low amplitud
35	4.5	28.88	normal	Mild background activity	80	normal
36	14	24.33	Bilateral occipito-parieto-frontal	normal	35	normal
37	120	27.35	normal	normal	28	Bilateral prolonged latency
38	46	37.62	Bilateral occipito-parietal,	Moderate background activity	39	Bilateral low amplitude

The PA levels in profoundly, profound-moderately, moderately and mildly retarded children and near-normal children were 34.61±6.45, mg/dL, 28.88±4.71 mg/dL, 25.28±4.71 mg/dL 22.86±2.65 mg/dL and 19.53±1.33 mg/dL in respectively. There were statistically significant correlation between plasma levels of PA at diagnosis and IQ levels. The high plasma PA levels were associated with low IQ scores ($p<0.001$) (Table 2). There were statistically significant correlation between the age at diagnosis and IQ scores. Late-diagnosed children had low IQ scores ($p<0.001$)(Table 2).

Table 2. The relation between plasma PA values, age at diagnosis and MRI, EEG,VEP abnormalities.

Neurological studies	Number and percentage of patients	Plasma PA levels at diagnosis(mg/dL)	P value	Age at diagnosis (months)	P value
Pathological MRI	20(52.6%)	30.2±4.2	P<0.001	45.1±33.9	p>0.005
Normal MRI	17(44.7%)	19.4±2.4		12.7±6.7	
Pathological EEG	23(60.5%)	29.4±5.1	P<0.001	39.1±33.0	P<0.001
Normal EEG	15(39.5%)	19.0±2.5		15.0±12.0	
Pathological VEP	25(65.7%)	28.6±5.6	P<0.001	40.2±32.6	P<0.001
Normal VEP	13(34.2%)	19.0±2.1		12.0±8.5	

Seventeen patients (44.7%) had normal MRI scans, 20 patients (52.6 %) had various degrees of white matter signal abnormalities in different locations on T2-weighted images. The high levels of PA were associated more serious white matter signal abnormalities on MRI ($p<0.001$) (Table 2). But there were no relationship between the pathologic MRI findings and age of patient at diagnosis ($p>0.05$) (Table 2). Among 23 patients who were younger than two years at diagnosis thirteen patients (54.1%) had white matter abnormalities on MRI although, among 15 patients who were older than two years at diagnosis 8 patients (53.3%) did not have any MRI findings.

Among 38 late-diagnosed PKU patients 15 patients (39.5%) had normal EEG. 23 patients (60.5%) had various degrees of EEG abnormalities. Eight patients (21%) had generalized EEG slowing and mild background abnormalities. Six patients (15.7%) had moderate background abnormalities. Eleven patients (28.9%) had generalized active epileptiform activity. Two patients(5.2%) had bioelectric status. One patient (2.6%) had hypsarrhythmic pattern . Despite the high incidence of abnormal EEG patterns only eight patients (21.1%) had epilepsy and seizures were controlled with monotherapy.

All patients revealed normal ophthalmologic examination and no visual complaints. Latency of VEP was prolonged in 11 patients (28.9%) and amplitude of VEP were reduced in 4 patients (31.6%). Prolongation of latency were observed in 11 patients (28.9%), and reduction of amplitude was observed in four patients (10.5%) . Ten patients had both low amplitude and prolongation of latency (26.3%). Thirteen patients had (34.2%) normal VEP findings.

DISCUSSION

PKU is the most commonly seen inherited metabolic disease in Turkey. The screening program was launched in 1993 in Turkey. Before the screening program was initiated and covered the whole country for PKU several late-diagnosed children were observed. Also after the beginning of screening program a few late-diagnosed patients were still been observed. Neurotoxicity of PA can manifest itself in at least two ways. First it may occur in brain white matter, where changes visible by MRI and are apparently more prevalent than overt neurological dysfunction; these changes occur in pressured to be well-treated patients and patients with only moderate chronic elevations of plasma phenylalanine. Second in the IQ scores of PKU patients in whom the values are disturbed below the normal range. These findings suggest that the putative threshold value for plasma PA is different for chronic and acute effects on brain[15]. In 1991 the progress of 51 never treated PKU patients during 22 years was reported. In that study one quarter of the patients had seizures, half were profoundly mental retarded and half were moderately impaired[16]. In our patients' group there was a positive correlation between the intensity of myelin defect and high plasma PA levels ($P<0.001$) (table 2). As in our study a positive relationship between the degree of MRI abnormality and biochemical severity was demonstrated in previous studies[9,17-19]. The supratentorial brain white matter is known to be primarily involved in phenylketonuria as has already been extensively reported in children, adolescents, and adults with PKU[9,17-19], even in patients with an early strict dietary control .

Koch and coworkers reported delay of myelination (all lobes), at autopsy, in a 4-month-old boy born to a woman with maternal PKU and high PA levels during pregnancy[20], thus underlying the link between high blood levels of PA and white matter involvement. MRI abnormalities in our patients' group were an increased signal in T2-weighted images and cortical atrophy. The distribution of affected areas were most commonly occipital and parietal regions in milder cases. These lesions were extended into frontal and temporal lobes in more severe cases. Previously these locations were defined in different studies in patients with both early and late-diagnosed PKU patients[9,21,22]. The quality and duration of long-term biochemical control influences the intellectual outcome, which is close to normal in patients with early and strict treatment. Also in late diagnosed patients it is stated that neurological outcome is mainly influenced by the age of treatment started[13]. The relationship between cognitive outcome and blood PA concentrations is well established. A systematic meta-analysis has documented a proportional relationship between the PA level and IQ[23]. In our study there was a positive correlation between the loss of IQ score and plasma PA levels ($p<0.001$)(table 2) and late-diagnosed children had low IQ scores ($p<0.001$) (Table 2).

Rolle- Daya detected various degrees of EEG abnormalities even in early-treated children and normal EEG patterns in 31 % of patients diagnosed after the age of six months[24]. The most common EEG abnormalities in PKU were background abnormalities and paroxysmal discharges[16,24]. In a review about EEG recording of PKU patients it was demonstrated that about 45% of the patients had an abnormal EEG and nearly 30% had a normal EEG in the beginning which became abnormal later[25]. An other study with 105 early-detected PKU patients showed that 52.3 % of the patients had seizures, but 66.6% had an abnormal electroencephalogram, which means some PKU patients had an abnormal EEG without any clinical seizure[26]. In our study although 60.5 % of patients had EEG abnormalities only 21.1 % patients had epilepsy. The most common detected EEG abnormality in our study was generalized EEG slowing and moderate background abnormality.

Jones et al demonstrated VEP abnormalities even in more than 80 % of early-diagnosed children and adults with PKU, with a significant reduction of amplitude and prolongation of latency despite the absence of visual symptoms and abnormalities on routine neuro-ophthalmalogical examination. Also in that study an important correlation between VEP, IQ scores and white matter abnormalities was demostrated[12]. Although in our patients routine neuro-ophthalmological examination was normal, and any patient had visual complaints 25 of them had VEP abnormalities such as reduction in amplitude, prolongation of latency or both.

PKU is not curable. However, if PKU is diagnosed early enough, an affected newborn can grow up with normal brain development. To prevent intellectual and neurological complications early diagnosis is important. Also High phenylalanine concentrations and late diagnosis appear to cause subclinical visual impairment and epilepsy. Lower blood

concentration of phenylalanine should be maintaned for optimal neurodevelopment and visual development.

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