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Assessment of brain phenylalanine dynamics in phenylketonuria patients

Ocena dynamiki mózgowego stężenia fenyloalaniny u pacjentów z fenyloketonurią

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Summary

Background: Phenylketonuria (PKU) is the most common inborn error of metabolism in man. Brain phenylalanine kinetics can determine neurological treatment outcome in phenylketonuria. The aim of our study was to test a simplified magnetic resonance spectroscopy method for assessment of brain phenylalanine dynamics in PKU patients.

Material/Methods: Brain phenylalanine concentration (measured by means of magnetic resonance spectroscopy) and blood phenylalanine concentrations changes occurring within 24 hours after oral phenylalanine loading were analyzed in 5 PKU patients.

Results/Conclusions: The brain/blood phenylalanine ratio in 3 persons with normal intelligence was lower than in 2 with borderline intelligence or mild mental retardation. In our opinion the proposed method could be useful for assessment of brain phenylalanine dynamics in PKU patients.

Key words: blood-brain barrier • amino acid transport

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Background

Phenylketonuria (PKU) is the most common disorder of amino acid metabolism in man. Treatment consists in life-long restriction of dietary phenylalanine intake to decrease its blood concentration as uncontrolled hyperphenylalaninemia could be toxic for the brain. The neuropathologic changes in the brain include hypomyelination diffuse gliosis and in some cases progressive white matter degeneration. Usually untreated patients are severely mentally retarded.

Interestingly, some persons with PKU who were never treated do not show neurological impairment. Several authors pointed that individual brain phenylalanine kinetics can determine neurological treatment outcome in phenylketonuria [1, 2] and low brain phenylalanine concentration despite hyperphenylalaninemia is probably crucial for the favorable outcome in such exceptional individuals. Thus, measurement of brain phenylalanine concentration in PKU – patients could be useful. The method of noninvasive assessment of brain phenylalanine by means of magnetic resonance spectroscopy (MRS) was described earlier. This technique requires, however, sophisticated determination of a "normal range" of the brain spectrum in a homogenous control group of healthy persons and, although reliable in adults, it is of limited use in children because of possible

Table 1. Study participants and results.
Tabela 1. Uczestnicy badania i uzyskane wyniki.

Case	Age/sex	IQ	Brain phenylalanine decrease (mmol/kg wet weight)	Blood phenylalanine change (mmol/l)		Brain/blood phenylalanine ratio
				1st day	2nd day	
1	16/M	134	0.046	1.69	1.51	0.25
2	15/F	90	-0.05	1.64	1.85	0.24
3	12/F	96	0.038	1.74	1.57	0.22
4	11/F	75	0.14	1.45	1.18	0.52
5	15/M	65	0.1	1.36	1.09	0.37

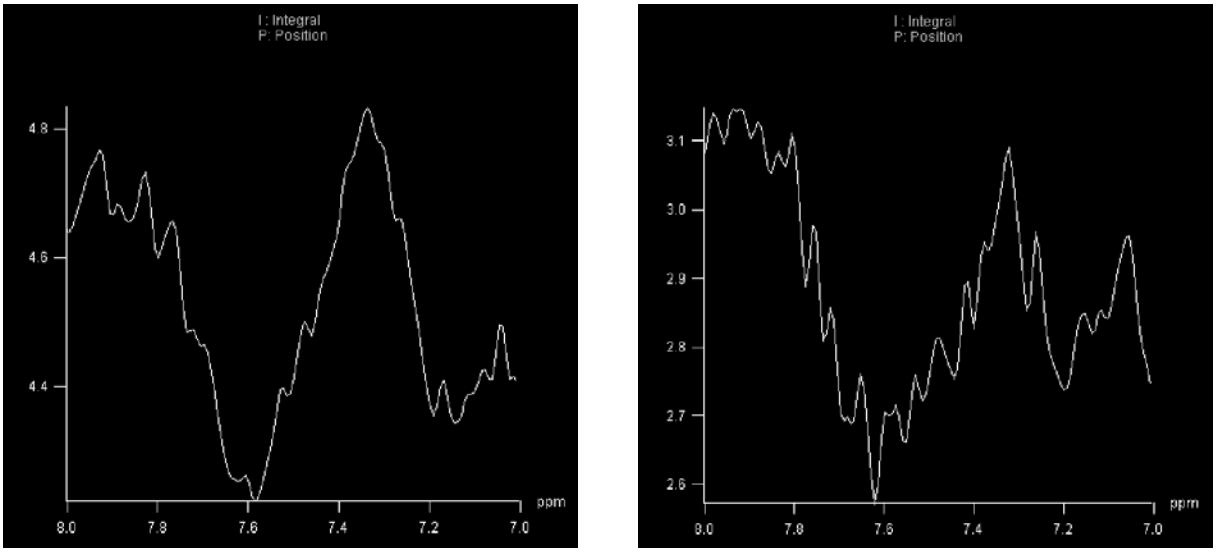

Figure 1. Brain spectrum (MRS) in a PKU patient (left) and a healthy individual (right). Phe signal at 7.37 ppm.
Rycina 1. Mózgowe spektrum (MRS) u pacjenta z PKU (po lewej) i u osoby zdrowej (po prawej). Sygnał fenyloalaniny przy 7,37 ppm.

age-related differences between brains of patients. We therefore intended to test a simplified age-independent method for analysis of brain phenylalanine dynamics in PKU – patients.

Material and Methods

Oral phenylalanine loading (100 mg/kg) with subsequent analysis of plasma phenylalanine concentration (colorimetry) and parallel brain MRS after 12 hours (first day) and 36 hours (second day) was performed in 5 early treated PKU – teenagers. MRS was conducted on a 1.5 T scanner (Magnetom Vision Plus, Siemens) with use of the PRESS (point resolved spectroscopy) technique, signal acquisition from a volume of 18 cm^3 of brain white matter, relaxation time/echo time 1500/30 ms and 512 acquisitions. Phenylalanine signal was identified at 7.37 ppm and creatine signal which served as an internal standard at 3.03 ppm. The molar change in brain phenylalanine concentration (Δ Phe_{Brain}) was calculated from equation: Δ Phe_{Brain} = 6.4 mmol/kg x [$Phe_{1st\ day}$ peak area /$Creatine_{1st\ day}$ peak area – $Phe_{2nd\ day}$ peak area /$Creatine_{2nd\ day}$ peak area] x 3/5, as the phenylalanine resonance is due to 5 protons and the creatine to 3 and with assumption of typical white matter creatine concentration of 6.4 mmol/kg of wet weight [3].

Results

Δ Phe_{Brain} / Δ Phe_{Blood} ratio describing the dynamics of brain phenylalanine concentration change during parallel blood phenylalanine change varied from 0.22 to 0.52. Interestingly in 3 persons with normal intelligence it was lower (0.22-0.25) than in 2 with borderline intelligence or mild mental retardation (0.37 and 0.52 respectively). Our results seem to be in agreement with the results obtained by others [1, 2] and in our opinion the proposed method could be useful for assessment of brain phenylalanine dynamics in patients with PKU. Detailed data on participants are given in table 1. Figure 1 shows brain spectrum (MRS) of a PKU – patient and of a healthy person.

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