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THE INCIDENCE OF TETRAHYDROBIOPTERIN SYNTHASE DEFICIENCY IN NORTHERN CHINESE POPULATION AND OUTCOME OF LATE-TREATED PATIENTS

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Objective: To get the incidence and to evaluate the treatment and outcome of late treated patients with tetrahydrobiopterin synthase (BH_4) deficiency in Northern Chinese population. **Methods**: From 1992 to 2005, a total of 889 patients with HPA were diagnosed in Northern China. After differential diagnosis, patients with BH_4 deficiency were treated with BH_4, levodopa and 5-hydroxytryptophane (5-HTP) immediately. Their blood phenylalanine levels, psychomotor and intelligence development were followed up. **Results**: A total of 61 cases were diagnosed as BH_4 deficiency, all of them were revealed as 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency. Among 569 cases of HPA detected by neonatal screening, PTPS deficiency was the cause in 41 patients giving a frequency of BH_4 deficiency as a cause of HPA of 7.2%. Their age at diagnosis were 2.1 months ~ 13 years. Due to the neonatal screening, the rate of late diagnosed BH_4 deficient patients were decreasing year by year. Forty-two patients were treated within 6 months and their development were normal or nearly normal. The rest 19 late-treated patients lived in community care home for people with learning disability before diagnosis. Even after treatment for 18–119 months, 2 (11%) were not fully ambulant, 7 (36%) were non-verbal, 13 (78%) had significant challenging behaviour, and up to 4 (21%) had epilepsy. **Conclusions**: The incidence of BH_4 deficiency among patients with HPA in Northern China is 7.2%, much lower than that in Southern China, and PTPS deficiency is the most common form of BH_4 deficiency. Development cannot benefit a lot from treatment in late-treated patients.

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CHARACTERISTICS OF DIETARY TREATMENT OF PKU IN DIFFERENT REGION OF CHINA

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China is such a large country that each region is characterized with its own local natural food. Due to the versatile diet structure and economic restraint, it is very difficult for the patients from different areas to follow identical diet as in European countries. Even the same food, if cultivated in different area, could have different content of phenylalanine (phe) and other nutrient. Since 2000, 37 patients in good compliance but with higher phe levels were transferred to our department from other neonatal screening centers. **Objective**: To identify the contents of natural food available in different regions of China and their effects on plasma phe levels and body growth. **Method**: We remodeled the diet structure according to the specific contents of phenylalanine, other amino acids, lipids and carbohydrates of the food in each patient's own hometown. The plasma amino acids levels before and after treatment were determined by using the amino acid analyzer. Body and mental development were followed-up. **Results**: Plasma phe levels in 32 patients were controlled within 2–6 mg/dl after the adjustment of their daily diet. Significant decrease were observed on plasma phe levels before and after treatment (580.9 ± 178.6) μmol/L, (226.5 ± 75.4) μmol/L respectively ($p < 0.01$), while other necessary amino acids levels greatly improved ($p < 0.01$). These patients presented nearly normal physical and intellectual development after five-year follow-up. **Conclusion**: Exact measurements of phe should be done in natural food in different regions especially in patients with good compliance by higher phe levels. High plasma phe level inhibit absorption of other amino acids from digestive system.

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QUALITY OF LIFE ASSESSMENT IN ADULT PKU-PATIENTS RETURNING TO LOW-PHENYLALANINE DIET

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Phenylketonuria (PKU) is the most common treatable disorder of amino acid metabolism in man. Treatment consists in the restriction of dietary phenylalanine intake. Low compliance or discontinuation of dietary therapy in majority of adults can lead to neuropsychological abnormalities and emotional problems. Thus, the aim of this survey was to assess the quality of life in patients who discontinued or significantly relaxed the diet, in a hope to collect data which could help to stimulate their diet resumption. **Methods**: Adult PKU-patients having classic phenylketonuria were tested by means of modified Psychological General Well-Being Index to assess their quality of life. The participants answered 21 questions concerning their anxiety, depressed mood, sense of positive well-being, self-control, general health and vitality and received 0–5 points for each answer. Cut-off points for the total score were 0–57 (severe distress), 58–68 (moderate distress) and 69–105 (positive well-being). **Results and conclusion**: 48 patients with PKU were included into the study. The results they achieved ranged from 30 to 94 points (severe distress in 16%, moderate distress in 37%, positive well-being in 47% of participants). Our results suggest, therefore, that interpersonal differences exist between the adult patients on relaxed diet, in part of whom quality of life often remains good, but who can also suffer from severe emotional distress. Returning to strict diet should be recommended especially for the last group of patients, despite typical compliance problems.

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PHENYLALANINE HAS DIFFERENT EFFECTS ON Rac1, Cdc42 AND RhoA EXPRESSION AND ACTIVITY IN CULTURED CORTICAL NEURONS

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Objective: Phenylketonuria (PKU) is characterized by high concentration of phenylalanine and mental retardation (MR). Pathologic changes in the brain of untreated PKU patients are reductions or abnormalities in axons, dendrites and synapses, which are thought to be due to toxic effects of phenylalanine and/or its metabolites. The mechanisms underlying impaired brain development and cerebral dysfunction by phenylalanine 'toxicity' remain unclear. Rho GTPases (Rac1, Cdc42, RhoA) are key signaling proteins that regulate neurite growth and synaptic connectivity. This study aimed to examine the role of Rho GTPases in neuronal injury induced by phenylalanine. **Methods**: Primary cultures of neurons were fixed and double-immunostained with anti-MAP2 and anti-tau1. The number of dendrites and spines were counted. Real time PCR and Western blot analysis were used to evaluate the Rho GTPases mRNA and protein expression. Rho GTPases activities were measured by GST pull down assay. **Results**: We had demonstrated that phenylalanine induced the reduction in number of primary dendrites and dendritic branches and spine density in cultured neurons. We discovered that phenylalanine down-regulated Rac1, Cdc42, RhoA mRNA and protein expression. Pull down assay showed that phenylalanine decreased Cdc42/Rac1 activity with time dependent, but increased RhoA activity. **Conclusions**: We had demonstrated that high concentration of phenylalanine effected the mRNA and protein expression and activity of Rac1, Cdc42 and RhoA. These results may provide important insights into the molecular mechanism underlying abnormality of dendrites and dendritic spines induced by phenylalanine, and probably are one of complicated mechanism of neuronal injury induced by phenylalanine.