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IS THERE A RISK TO OVERESTIMATE A POSITIVE BH_4 LOADING RESPONSE PERFORMED IN THE NEONATAL PERIOD?

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Background/Methods: A BH_4 loading test was performed in a 9-day-old boy with PKU, later genetically verified (Y414C, R210Q).
Results: The result was excellent, FA values declining from 1270 μmol/L to 340 μmol/L after 8 h (> 70% reduction) with full breast feeding. BH_4 therapy, 10 mg/kg/day was started. During the first 6 months the FA levels were kept well within the therapeutic range. At 4 months of age, solid food was introduced and the FA levels eventually increased. At 7 months of age the BH_4 dose was adjusted to correspond to 10 mg/kg/day. This only marginally improved the FA concentrations. Despite a further increase of BH_4 to 15 mg/kg/day at the age of 9 months, the boy continued to have too high FA levels, necessitating the introduction of protein restricted diet.

The boy has had a normal growth velocity apart from the first 6 weeks of life when his weight gain was above average.
Conclusions: A newborn child is catabolic during the first days of life, gradually changing to an anabolic state and increasing growth velocity in infancy. Hence, the result from a BH_4 loading test in the neonatal period may be overestimated as it coincides with the increase in growth. The prognostic information to the parents may thus be overoptimistic. The relatively low protein content in breast milk compared to solid foods may maintain a good metabolic control during the first months of life. However, when the child gets older protein restriction may be necessary

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THE SCREENING FOR TETRAHYDROBIOPTERIN METABOLIC DISORDERS AND RELATED GENE ANALYSIS AMONG THE PATIENTS WITH MOTOR DISTURBANCE AND MENTAL RETARDATION

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Objective: To get the incidence of various enzyme deficiency in tetrahydrobiopterin (BH_4) metabolism among the patients with motor disturbance and mental retardation and the analysis of related gene mutation.
Methods: One hundred patients (4 months–14 years) with unknown motor and mental retardation were referred to this study. All patients were performed by phenylalanine (Phe) (100 mg/kg) or combined with BH_4 (20 mg/kg) loading test, the analysis of urinary pterin and dihydropteridine reductase (DHPR) activity. Some patients suspected as dopa-responsive dystonia (DRD) were treated with dopa for diagnosis. The mutation analysis of GTP cyclohydrolase 1 gene (*GCH1*) and 6-pyruvoyl tetrahydropterin synthase gene (*PTS*) were done for the parents with DRD and PTPSD.
Results: Seventy of 100 patients had normal basic blood Phe levels, 16 of 70 cases were received the treatment of dopa 50–300 mg/d, 6 (6%) were diagnosed as DRD. The other thirty patients had hyperphenylalaninemia(HPA) (Phe 1022 ± 290 mmol/L). 8 (8%) patients were diagnosed as PTPS deficiency. Their Phe concentrations remarkably decreased after BH_4 loading, and urinary biopterin percentage were $1.2 \pm 1.0\%$. Twenty-two (22%) HPA patients were diagnosed as phenylalanine hydroxylase (PAH) deficiency. The mutations IVS5 +3insT of *GCH1* gene were found in 2 patients with DRD and the 7 kind of PTPS mutations (166G>A, 259C>T, 286G>A, 155A>G, 430G>C, 276T>A, 393A>C) were found in 8 patients with PTPSD.
Conclusions: Some patients with unknown motor disturbance and mental retardation may suffer from BH_4 metabolism related diseases. Theses patients are necessary to be screened for such kind of diseases in order to receiving the appropriate treatment.

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A NEW PRESENTATION OF 6-PYRUVOYL TETRAHYDROPTERIN SYNTHASE (PTPS) DEFICIENCY – DOPA RESPONSIVE DYSTONIA (DRD)

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PTPS deficiency typically presents asymptomatically via newborn screening or with progressive mental and physical retardation with extra-pyramidal signs, epilepsy and lighter pigmentation. In Hong Kong, there is no mass newborn screening for inborn error of metabolism like hyperphenylalanaemia. We report a patient with PTPS deficiency who presented with DRD. She was the first child of a non-consanguineous Chinese couple with uneventful perinatal period. There is no relevant family history. Since 9 months of age, she started to have episodic tremor with eye starring. This happened few times per month. She was treated as epilepsy but the condition did not improve with anticonvulsants. In early childhood and was noted to have dysarthria with dystonia and rigidity of both the upper limbs. There was diurnal fluctuation. She has normal intelligence. L-dopa was started and was kept at a dose of 5 mg/kg/day. All her symptoms resolved. She is now 16 years old. Cerebrospinal fluid (CSF) for neurotransmitter assays was done after stopping L-dopa for 5 days. She then developed generalized dystonia and parkinsonism with swallowing difficulty. Her baseline phenylalanine was 179 μmol/L (normal 30–90). CSF revealed a low biopterin, homovanillic acid, 5-hydroxyindoleacetic acid level and a high neopterin level. The pattern was compatible with PTPS deficiency. This was confirmed with genetic mutation study. We therefore recommend screening plasma phenylalanine level and CSF neurotransmitter assays for all patients with DRD.

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LONG-TERM FOLLOW-UP OF TAIWAN CHINESE PATIENTS WHO RECEIVED EARLY TREATMENT FOR 6-PYRUVOYL-TETRAHYDROPTERIN SYNTHASE DEFICIENCY

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Background: The reports of the outcomes of patients who received early treatment for 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency, particularly over long periods of observation, remain scarce. Quite a few PTPS patients, even though detected by newborn screening and given early treatment still had unsatisfactory outcomes. In Taiwan, the prevalence of PTPS deficiency ($\approx 1/100\,000$) is considerably higher than in Caucasian populations. This provides us with more opportunities to observe and treat this form of illness within a single medical center.
Methods: We reviewed the IQ outcomes of all of our PTPS deficiency patients who were found by the newborn screening and received an early treatment. The possible factors related to outcomes such as genotypes, peak level of phenylalanine and the levels of urinary pterin at diagnosis, birth body weight, and the timing and dosages of administered BH_4 and neurotransmitters were also analyzed in this study.
Results: All of our patients achieved a normal IQ, even though we just based treatment dosage on clinical response and adverse effects of the neurotransmitters, without monitoring the levels of the CSF neurotransmitter metabolites during the administration of neurotransmitters. The average intelligence quotient (IQ) score of our PTPS patients is 97 ± 10, which is much better than other previous reports. In this study we also found genotype, birth body weight and treatment starting age are related to the IQ outcomes.
Conclusions: An effective newborn screening referral system and an early adequate therapy can still achieve a normal IQ outcome in PTPS patients, even if the prenatal brain impairment has existed.