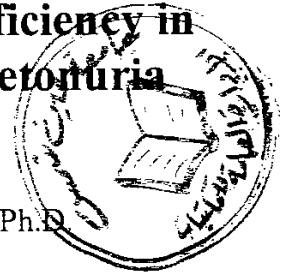


AIN SHAMS UNIVERSITY
INSTITUTE OF POST GRADUATE
CHILDHOOD STUDIES
MEDICAL DEPARTMENT

Tetrahydrobiopterin Deficiency in Patients With Phenylketonuria

Submitted in Fulfillment of Ph.D
In Childhood Studies
Medical Department

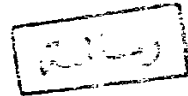


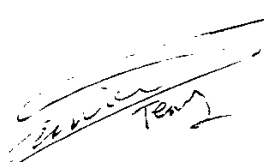
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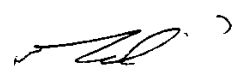
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To My Family

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List of abbreviations

| | |
|-------------------------|--|
| AIDS | Acquired immuno-deficiency syndrome |
| APM | Aspartame |
| ATP | Adenosine triphosphate |
| BH2 | Dihydropterin |
| BH4 | Tetrahydrobiopterin. |
| BMD | Bone mineral density |
| CDG | Carbohydrate deficiency glycoprotein |
| CHO | Carbohydrate |
| CNS | Central nervous system |
| CO2 | Carbon dioxide |
| CSF | Cerebrospinal fluid |
| CT | Computed tomography |
| DGGE | Denaturing gradient gel electrophoresis |
| DHPR | Dihydropteridine |
| DNA | Deoxyribonucleotide |
| DNPH | Dinitrophenylhydrazine |
| DXA | Dual-energy X-ray absorption |
| EEG | Electroencephalography |
| FAO | Fatty acid oxidation defects. |
| FDP | Fructose diphosphatase |
| FeCl₃ | Ferric chloride |
| G6P | Glucose-6-phosphate |
| GTP | Guanosine triphosphate |
| GTP-CH | Guanosin triphosphate cyclohydrolax |
| HMG-CoA | 3-Hydroxy-3-Methylglutaryl coenzyme A |
| HPLC | High performance liquid chromatography |
| IEM | Inborn error of metabolism |
| IQ | Intelligent quotient |
| I.V. | Intravenous |
| KCl | Potassium chloride |
| LC | Liquid chromatography |

| | |
|------------------------|---|
| MR | Mental Retardation |
| MRI | Magnetic Resonant Imaging |
| MSUD | Maple syrup urine disease |
| ND | Not done |
| NKH | Nonketotic Hyperglycemia |
| P | Short arm of chromosome |
| PAH | Phenylalanine hydroxylase |
| PAL | Phenylalanine ammonia liase |
| PCD | Pterin Carbinolamine dehydratase |
| PCR | Polymerase chain reaction |
| PEPCK | Phosphoenolpyruvate carboxykinase |
| PH | Phenylalanine hydroxylase |
| Phe | Phenylalanine |
| PKU | Phenylketonuria. |
| PTS, PTPS | Pyruvoyl-tetrahydropterin synthase |
| q | Long arm of chromosome |
| RBC_s | Red Blood Corpuscles |
| RFLP | Restriction fragment length polymorphism |
| RNA | Ribonucleic acid |
| SAH | S.adenosyl homocysteine hydrolase |
| SBMD | Spine bone mineral density |
| SD | Standard deviation |
| SO | Sulfite Oxidase deficiency |
| Syn | Syndrome |
| TBMD | Total body bone mineral density |
| TLC | Thin layer chromatography |
| UK | United Kingdom |
| USA | United States of America |
| VEP | Visual evoked potential |
| VNTR | Variable number of tandem repeats |

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INTRODUCTION

Introduction

Inborn errors of metabolism are individually rare, but collectively numerous. Many general practitioners and pediatricians only think of IEM in very unspecific clinical circumstances such as psychomotor retardation or seizures, they ignore most of the highly specific symptoms which are excellent keys to the diagnosis. Although most genetic metabolic errors are hereditary and transmitted as recessive disorders, the majority of cases appear sporadic, because of the small size of siblings in developed countries. Hereditary does not mean "congenital" and many patients can present a late onset form in childhood, adolescence or even adulthood [Burton, 1987].

One of the more common IEM is hyperphenylalaninemia which is mostly due to a defect in the hepatic enzyme phenylalanine hydroxylase, which catalyzes the conversion of phenylalanine to tyrosine. As a result, concentrations of phenylalanine increase relative to tyrosine in blood and other body fluids. A parallel increase occurs in the production and excretion of phenylketones and phenylamines [Scriver, et al., 1995].

The term phenylketonuria is often reserved, rather illogically, for more severe forms of deficiency in the enzyme phenylalanine hydroxylase in which urinary phenylketones are easy to detect by simple chemical methods [Kaufman, 1987].

The exact pathogenesis is not clear, but failure of myelination and of brain development is thought to underlie

the mental retardation, impaired melanin synthesis is believed to be responsible for the lighter than expected pigmentation of PKU patients.

Other variants of classic PKU detected in the neonatal period include mild PKU and hyperphenylalaninaemia. [Okano, et al., 1991].

Tetrahydrobiopterin deficiency, a variant of hyperphenylalaninaemia are very heterogenous ranging from mild forms requiring only marginal if any treatment to severe forms which are in some cases very difficult to treat. All variants of tetrahydrobiopterin deficiency can be differentiated from the classical PKU by measurement of pterin metabolites in patients' urine, tetrahydrobiopterin loading test and by dihydropteridine reductase activity in erythrocytes from the Guthrie card [Blau, et al., 1996]. Because patients in the two groups require different treatment to prevent irreversible neurological damage, tetrahydrobiopterin deficiency among newborns with hyperphenylalaninaemia must be rapidly diagnosed and distinguished from classic PKU [Blau, 1988; Dhondt, 1991].

The following enzyme defects are known to cause tetrahydrobiopterin - dependent hyperphenylalaninemia [Blau et al., 1989; Scriver et al., 1995]:

- GTP cyclohydrolase
- 6-pyruvoyltetrahydropterin synthase
- Dihydropteridine reductase
- Carbinolamine dehydratase deficiency.

Recently, it has been recommended that a low phenylalanine diet for life should be introduced to patients