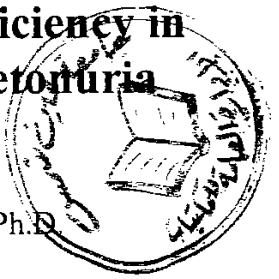
AIN SHAMS UNIVERSITY
INSTITUTE OF POST GRADUATE
CHILDHOOD STUDIES
MEDICAL DEPARTMENT

Tetrahydrobiopterin Deficiency in Patients With PhenylKetonuria



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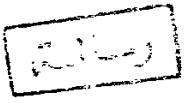
By
Amira Mohamed Diaa ElDin ElTantawy

Supervised By



Dr. Samia A.Temtamy
Professor of Human Genetics
National Research Center

Dr. Mohamed ElSawi
Professor in Paediatrics
Department "Genetic Unit"
Ain Shams University

Dr. Ikram Fateen
Assisstant Professor of Biochemistry
National Research Center

1998

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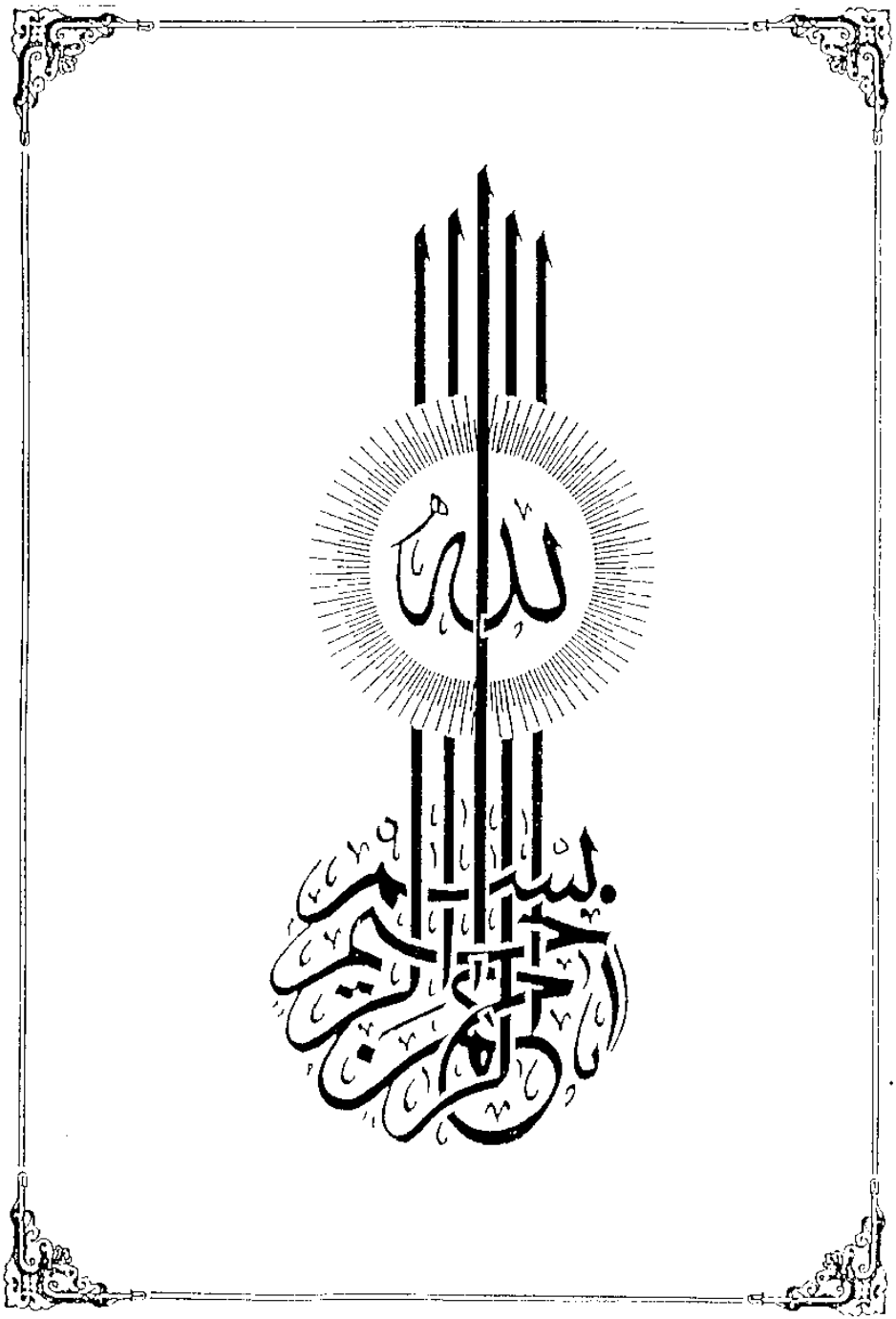

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To My Family

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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	Denaturating 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
$FeCl_3$	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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NTRODUCTION

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].**

Tetrahydrobiopetrin 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