Prevalence of inborn errors of amino acid metabolism among Egyptians in the Genetic Unit, Pediatric Department, Ain Shams University from January 2007 to June 2013

Thesis

Submitted for partial fulfillment of the requirements of master Degree of Medical & Clinical Genetics

By

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2014

Acknowledgment

First thanks to **ALLAH** *to whom I relate any success in achieving any work in my life.*

I would like to express my sincere appreciation and deep gratitude to Prof. Dr. Mohamed El Sawy. Professor in Pediatric Department and Genetic Unit, Faculty of Medicine, Ain Shams University, Dr. Osama Zaki, Consultant of Medical & Clinical Genetics, Faculty of Medicine, Ain Shams University, for their helpful supervision and valuable instructions through this work.

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INTRODUCTION

Inborn errors of metabolism (IEM) constitute a highly heterogeneous category of rare diseases, representing a relevant cause of morbidity and mortality **(Dionisi-Vici 2002)**.

IEM result from enzymatic defects of the intermediary metabolism pathway which result in the accumulation of one or more amino/organic acid and/or metabolites. The biochemical hallmarks of these disorders can be detected by tandem mass spectrometry (MS/MS) **(Burlina 1999)**.

Many of the inborn errors of metabolism, including certain disorders of amino acid metabolism, present in the young infant with symptoms of an acute or chronic metabolic encephalopathy. Typical symptoms include lethargy, poor feeding, apnea or tachypnea, and recurrent vomiting ***(Burton, 1998)*.**

They present clinically in a variety of ways, involving virtually any organ or tissue of the body, and accurate diagnosis is important both for treatment and prevention of disease in other family members ***(Clarke, 2006)*.**

The introduction of tandem mass spectrometry to newborn screening has greatly expanded the potential number

of disorders detectable in the neonatal period by at the presymptomatic stage ***(Wilcken et al., 2003)*.**

There are a few Arab countries in the Middle East and North Africa region that have started a NBS program, while others have either a limited hospital-based selective NBS program or have just completed pilot studies ***(Al-Gazali, 2006)*.**

AIM OF THE WORK

The main objectives:

Assessment of the overall prevalence rate of inborn errors of amino acid metabolism including phenyl-ketonuria, tyrosinemia, non ketotic hyperglycinemia and maple syrup urine disease in our Genetics Unit, Pediatric Hospital, Ain shams University.

Specific objectives:

To evaluate the clinical progress of the patients with IEM in relation to the available health services for them in our Genetics unit.

Chapter (1)

INBORN ERRORS OF METABOLISM

Inborn errors of metabolism (IEM) cause hereditary metabolic diseases (HMD) and they result from the lack of activity of one or more specific enzymes or defects in the transportation of proteins. The consequences can usually be the accumulation of substances present in small amounts, the deficiency of critical intermediary products, the deficiency of specific final products or furthermore the noxious excess of products of alternative metabolic pathways ***(Waber, 1990)*.**

Inborn errors of metabolism (IEM) seem to be common in the Middle East and North Africa, where high consanguinity rates still prevail due to frequents marriages between close relatives **(Teebi 2006).**

Among these IEM, aminoacidopathies (AAP) have a relatively high incidence ***(Sanderson et al., 2006)*.**

Amino acids are the building blocks of protein. Twenty amino acids are involved in metabolism. Each amino acid is further broken down into ammonia, carbon dioxide, and water. Disorders that affect the metabolism of amino acids include phenylketonuria, tyrosinemia,

homocystinuria, non ketotic hyperglycinemia and maple syrup urine disease. These disorders are autosomal recessive, and all may be diagnosed by analyzing amino acid concentrations in body fluids ***(Hoffmann, 2010)*.**

Aminoacidopathies are genetic disorders of amino acid metabolic pathways resulting in various biochemical disturbances and clinical manifestations ***(Scriver et al., 2001)*.**

Clinical manifestations presenting usually with variable neurological and digestive symptoms at different ages ***(Saudubray, 2012)*.**

The increasing application of new technologies such as tandem mass spectrometry (MS-MS) to newborn screening allows early identification of inborn errors of metabolisms. The disorders detected by tandem mass spectrometry generally include aminoacidopathies, urea cycle disorders, organic acidurias, and fatty acid oxidation disorders ***(Wilcken et al., 2003)*.**

At present, dietary management is the mainstay of treatment for most aminoacidopathies. Dietary treatment aims to prevent accumulation of the substrates and associated metabolites to toxic levels ***(Saudubray et al., 2006)*.**

This can be accomplished by natural protein restriction, combined with protein substitution with all amino acids except for the amino acids prior to the metabolic block and enriched with the amino acid that has become essential by the enzymatic defect ***(Camp et al., 2012)*.**

Chapter (2)

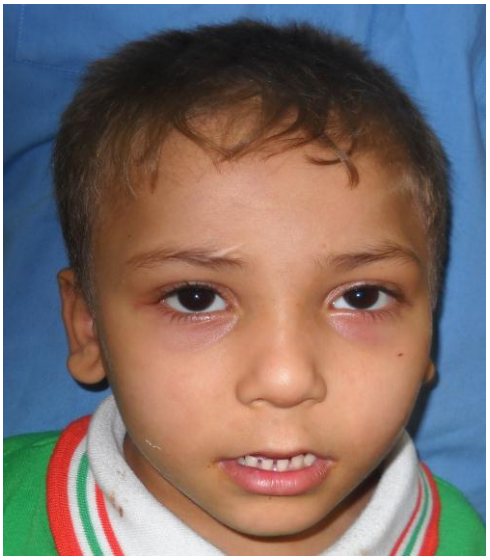
PHENYLKETONURIA

Phenylketonuria (PKU), which is the most common IEM, is caused by decreased activity of phenylalanine hydroxylase (PAH), an enzyme that converts the amino acid phenylalanine to tyrosine. Decreased PAH activity results in accumulation of phenylalanine and decreased amount of tyrosine and other metabolites ***(Hoffmann et al., 2010).***

In deficiency of this enzyme, phenylpyruvate (phenylketone) may be detected in the urine ***(Williams et al., 2011).***

Accumulation of phenylalanine in the body can cause damage to the central nervous system and subsequently cognitive and behavioral abnormalities and mental retardation in both children and adults ***(Mitchell et al., 2011).***

Remarkable clinical findings are light colored skin, hair and eyes, eczematous rash and behavioral disorders ***(Williams et al., 2011).***



Picture showing a case of PKU
(Genetics Unit, Ain Shams University)

The incidence of PKU varies in different populations, with a prevalence of 1 in 10,000 births in Europe and the United States ***(Dobrowolski et al., 2011)***.

Its prevalence is higher in northern Europeans and it has an incidence of 1 in 4,500 in the Irish ***(Blau et al., 2010)***.

With the average incidence of 1 per 10,000 newborns, PKU is considered to be the most common inborn error of amino acid metabolism in Caucasians and one of the most studied rare diseases ***(Scriver et al., 2008)***.