METABOLIC SCREENING IN NEONATE WITH RISK OF INBORN ERROR OF METABOLISM

Thesis

Submitted for Partial Fulfillment of Master Degree in Pediatrics

By

Samah El Yamani El Akhdar
M.B.B.Ch., Ain Shams University

Supervisors

Prof. Dr. Rabah Mohmmed Shawky
Prof. of Pediatrics and Genetics
Faculty of Medicine, Ain Shams University

Dr. Heba Salah Abd Al Khalek
Lecturer of Pediatrics and Genetics
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2014

List of Contents

List of Abbreviations

ACP	Acylcarnitine profile
ADHD	Attention – deficit/ hyperactivity disorder
AFP	Alpha fetoporotein
AGAT	Arginine-glycine amidinotransferase
AL	Argininosuccinate lyase
ARG1	Arginase 1
AS	Argininosuccinate
ASL	Argininosuccinate lyase
ASS1	Argininosuccinate synthetase
BCAAs	Branched chain amino acids
BCKAs	Branched-chain α-ketoacids
BCKDC	Branched -chain α-keto acid dehydrogenase complex
BH4	Tetrahydrobiopterin
Ca	Calcium
CBC	Complete blood count
CCDS	Cerebral creatine deficiency syndrome
CDG	Congenital glycosilation defects
CPS1	Carbamoyl-phosphate synthetase 1
CPS-1	carbamoyl-phosphate synthase I
CR TR	Creatine transporter
CRP	C- Reactive protein
CSF	Cerepro spinal fluid
CSF	Cerebrospinal fluid
CTLN2	Citrullinemia type II
CVD	Cardio vascular diseases
DBS	Dried blood spot
DIC	Disseminated intravascular coagulation

List of Abbreviations (Cont...)

DNA	Deoxyribonucleic acid
DNPH	Dinitrophenylhydrazine
E1	branched-chain α-ketoacid decarboxylase
E2	dihydrolipoyl transacylase
E3	dihydrolipoyl dehydrogenase
ELISA	Enzyme Linked Immunosorbant Assay
ESI	Electrospray ionization
FAB	Fast atom bombardment
FAO	Fatty acid oxidation disorder
FC	Free carnitine
FDA	Food and Drug Administration
FDP	Fibrin degradation product
FIB	Fast ion bombardment
GAMT	Guanidinoacetate methyltransferase
GC	Gas chromatographic
GGTP	γ-glutamyltranspeptidase
GM1	GM1 gangliosidoses
GSD	Glycogen storage disease
GTP	Guanosine triphosphate
HCU	Homocystinuria
HELLP yndrome	Hemolysis, Elevated Liver enzymes, Low Platelet count
HIE	Hypoxic ischemic encephalopathy
HMD	Hereditary metabolic diseases
HMG-CoA	Hydroxymethylglutaryl-CoA Lyase deficiency
HPA	Hyperphenylalaninaemia
HPLC	High performance liquid chromatography
IEM	Inborn error of metabolism

List of Abbreviations (Cont...)

IMD	Inherited metabolic disorder
IQ	Inelegant quality
K	Potassium
LC	Liquid Chromatography
LNAAs	Large natural amino acids
MADD	multiple acyl-CoA dehydrogenase deficiency
MCAD	Medium-chain acyl-CoA dehydrogenase deficiency
MPS	Mucopolysacridosis
MR	Mental retardation
MRM	Multiple reaction monitoring
MS	Metabolic screening
MS/MS	Tandem Mass Spectrometry
MSUD	Maple syrup urine disease
Na	Sodium
NAGS	N-acetylglutamate synthase
NBS	National newborn screening
NCG	N-carbamylglutamate
NENSP	New England Newborn Screening Program
NICCD	neonatal intrahepatic cholestasis caused by citrin deficiency
NICU	Neonate intensive care unite
NL	Natural loss
NTBC	2-nitro- 4- trifluoromethylbenzoyl)- 1,3-cyclohexanedione
OLT	orthotopic whole liver transplantation
OTC	Ornithine transcarbamylase
PAH	Phenylalanine hydroxlase
PAL	Phenylalanine ammonia- lyase

List of Abbreviations (Cont...)

Phe	Phenylalanine
PKU	phenylketonuria
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Qaulity control
SCAD	short-chain acyl-CoA dehydrogenase
TCA cycle	Tricarboxylic acid cycle
TMS	Tandem mass spectrometry
TNT	Transient neonatal tyrosinemia
Tyr	Tyrosine
UCD	Urea cycle defect
UPLC	Ultra-performance liquid chromatography
US	United states
VLCAD	Very long-chain acyl-CoA dehydrogenase deficiency
VLCFA	Very long chain fatty acids
XXth century	20th century
αKG	alpha-ketoglutarate
αKIC	(l alpha-ketoisocaproate
6-PTS	6-Pyruvoyltetrahydropterin

List of Tables

List of Tables (Cont...)

List of Figures

INTRODUCTION

Inborn error of metabolism (IEM) are rare genetic disorders in which the body cannot properly turn food into energy**(Kimberly, 2011).** Inborn errors of metabolism cause hereditary metabolic diseases (HMD) and classically they result from the lack of activity of one or more specific enzymes or defects in the transportation of proteins **(Martins, 1999) and (Bearn, and Miller, 1979).**

More than three hundred human diseases are known today that are caused by inborn errors of metabolism and this number is constantly growing because of new identification techniques for the various biochemical phenotypes. However, the detection of HMD incidence has not been increasing in parallel, probably because its diagnosis is being underestimated. Faulty diagnosis of IEM is related to a series of factors: (1) they are individually considered rare and therefore many physicians do not consider IEM until most frequent conditions have been ruled out, (2) blood and urine samples for investigation of metabolic errors need to be collected at the right time in relation to the course of the disease, and (3) many metabolic diseases only produce intermittent abnormalities **(Martins, 1999).**

IEM are not rare diseases when we observe their cumulative incidence, which is about one in every 5000 live

births. Nevertheless, the prevalence of each disease has many variables, especially relating to race. Examples of frequency for specific diseases include: 1 in 12, 000 for phenylketonuria; 1 in 15, 000 for organic acidurias **(Martins, 1999).**

The clinical picture may vary, infants with metabolic disorders typically present with lethargy, decreased feeding, vomiting, tachypnea (from acidosis), decreased perfusion, and seizures. As the metabolic illness progresses, there may be increasing stupor or coma associated with progressive abnormalities of tone (hypotonia, hypertonia), posture (fisting, opisthotonos), and movements (tongue-thrusting, lip-smacking, myoclonic jerks), and with sleep apnea. Metabolic screening tests should be initiated. Elevated plasma ammonia levels, hypoglycemia, and metabolic acidosis, if present, are suggestive of inborn errors of metabolism. In addition, the parent or physician may notice an unusual odor in an infant with certain inborn errors of metabolism (e.g., maple syrup urine disease, phenylketonuria [PKU], hepatorenal tyrosinemia type 1, isovaleric acidemia). A disorder similar to Reye's syndrome (i.e., nonspecific hepatic encephalopathy, possibly with hypoglycemia) may be present secondary to abnormalities of gluconeogenesis, fatty acid oxidation, the electron transport chain, or organic acids **(Talkad, and Raghuveer, 2006).**

Although inborn errors of metabolism are rarely found to be the cause of epilepsy, seizures are a frequent symptom in metabolic disorders. In a few of these, epilepsy responds to specific treatment by diet or supplementation**(Wolf et al., 2005).**

However, most of these disorders are treatable if they are diagnosed early. With early diagnosis and appropriate treatment, some problems can be avoided; these include biochemical disturbances such as hyperammonemia in patients with urea-cycle disorders that present after the newborn period, severe metabolic acidosis in patients with disorders of organic acids, or hypoketotic hypoglycemia, cardiomyopathy, or rhabdomyolysis in patients with disorders of fatty-acid oxidation; if left untreated, these disorders may lead to brain damage or other organ damage. Some cause severe illness or death within the first few days of life**(Wilcken, 2003).**

Newborn screening tests look for serious developmental, genetic, and metabolic disorders so that important action can be taken during the critical time before symptoms develop. Screening tests do not diagnose illnesses. They identify which babies need additional testing to confirm or rule out illnesses **(Kimberly, 2011).**

Screening tests are used to detect a number of disorders, including:

- Amino acid metabolism disorders:
  - Arginosuccinic acidemia
  - Citrullinemia
  - Homocystinuria
  - Maple syrup urine disease
  - Phenylketonuria (PKU)
  - Tyrosinemia type I
- Biotinidase deficiency
- Congenital adrenal hyperplasia
- Congenital hypothyroidism
- Cystic fibrosis
- Fatty acid metabolism disorders:
  - Carnitine uptake deficiency
  - Long-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency
  - Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
  - Trifunctional protein deficiency

- Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)

- Galactosemia **(Kimberly, 2011).**

Screening test is done by prick the baby's heel to obtain a few drops of blood. The blood is sent to a lab for analysis. Risks for the newborn heel prick blood sample include pain and possible bruising at the site where the blood was obtained **(Kimberly, 2011).**

AIM OF THE WORK

The aim of this work is to:

- Detect the incidence of IEM among neonates with risk factors
- Diagnose early IEM which are clinically important disorders in order to minimize morbidity and mortality