

# **METABOLIC SCREENING IN NEONATE WITH RISK OF INBORN ERROR OF METABOLISM**

*Thesis*

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*List of Abbreviations*

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

*List of Abbreviations (Cont...)*

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

*List of Abbreviations (Cont...)*

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

*List of Abbreviations (Cont...)*

<b>Phe</b> .....	Phenylalanine
<b>PKU</b> .....	phenylketonuria
<b>PT</b> .....	Prothrombin time
<b>PTT</b> .....	Partial thromboplastin time
<b>QC</b> .....	Quality control
<b>SCAD</b> .....	short-chain acyl-CoA dehydrogenase
<b>TCA cycle</b> .....	Tricarboxylic acid cycle
<b>TMS</b> .....	Tandem mass spectrometry
<b>TNT</b> .....	Transient neonatal tyrosinemia
<b>Tyr</b> .....	Tyrosine
<b>UCD</b> .....	Urea cycle defect
<b>UPLC</b> .....	Ultra-performance liquid chromatography
<b>US</b> .....	United states
<b>VLCAD</b> .....	Very long-chain acyl-CoA dehydrogenase deficiency
<b>VLCFA</b> .....	Very long chain fatty acids
<b>XXth century</b> .....	20th century
<b><math>\alpha</math>KG</b> .....	alpha-ketoglutarate
<b><math>\alpha</math>KIC</b> .....	( 1 alpha-ketoisocaproate
<b>6-PTS</b> .....	6-Pyruvoyltetrahydropterin

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## INTRODUCTION

**I**nborn 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 Raghuvver, 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