NEONATAL SCREENING

Review

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LIST OF ABBREVIATIONS

AABR : Automated Auditory Brainstem Response
AAP : American Academy of Pediatrics
AFLP : Acute Fatty Liver of Pregnancy
AFP : Alphafetoprotein
AIDS : Acquired Immunodeficiency Syndrome
AL : Argininosuccinic Acid Lyase
AOAE : Automated Otoacoustic Emissions
AS : Argininosuccinic Acid Synthetase
ASA : Argininosuccinic Acid
BCAA : Branched-Chain Amino Acids
BCKD : Branched-Chain α Ketoacid Dehydrogenase
BH4 : Tetrahydrobiopterin
BIA : Bacterial Inhibition Assay
BUN : Blood Urea Nitrogen
C/AT : carnitine/acylcarnitine translocase,
CAH : Congenital Adrenal Hyperplasia
CF : Cystic Fibrosis
CFTR : Cystic Fibrosis Transmembrane Conductance Regulator
CH : Congenital Hypothyroidism
CMV : Cytomegalovirus
CPS : Carbamyl Phosphate Synthetase
CPT : Carnitine Palmitoyl Transferase
ECMO : Extracorporeal Membrane Oxygenation
ESI : Electrospray Ionisation
FAO : Fatty Acid Oxidation
FAOD : Fatty Acid Oxidation Disorders
G6PD : Glucose-6-Phosphate Dehydrogenase Deficiency
GA1,GA2: Glutaric Acidemia, Type 1 and Type 2
GSD : Glycogen Storage Disease
HHH : Hyperornithinemia, Hyperammonemia, Homocitrullinuria
HMG : 3-Hydroxy-3-Methylglutaryl
HMP : Hexose Monophosphate

HRSA : Health Resources and Services Administration
IDD : Iodine Deficiency Disorders
IEMs : Inborn Errors of Metabolism
IgG-IFA : IgG Indirect Fluorescent-Antibody
IRT : Immunoreactive Trypsinogen
L/P : Lactate/Pyruvate Ratio
LCHAD : Long-Chain L-3-Hydroxyacyl CoA Dehydrogenase
LPI : Lysinuric Protein Intolerance
MCAD : Medium-Chain Acyl-CoA Dehydrogenase
MCC : 3-Methylcrotonyl CoA Carboxylase
MMA : Methylmalonic Acidemia
MSUD : Maple Syrup Urine Disease
NAGS : N-Acetyl Glutamate Synthase
NICU : Newborn Intensive Care Unit
OTC : Ornithine Transcarbamylase
PA : Propionic Acidemia
PAH : Phenylalanine Hydroxylase
PC : Pyruvate Carboxylase
PDH : Pyruvate Dehydrogenase
Phe : Phenylalanine
PKU : Phenylketonuria
PPHN : Persistent Pulmonary Hypertension of the Newborn
RBC : Red Blood Cell
SCAD : Short-Chain Acyl-CoA Dehydrogenase
SCD : Sickle Cell Disease
SIDS : Sudden Infants Death Syndrome
SV : Simple Virilizing
TFP : Trifunctional Protein
UCD : Urea Cycle Defects
VLCAD : Very-Long-Chain Acyl-CoA Dehydrogenase.

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INTRODUCTION

Most of genetic conditions screened for are rare diseases. One out of approximately 1,500 babies will be born with one of these conditions, many metabolic disorders are not recognized because of their rarity. Thousands of babies die each year of unexplained causes, such as sudden infant death syndrome (SIDS), up to 3% of babies diagnosed with SIDS actually died of metabolic disorders. The greatest problem with the recognition of inherited metabolic disease is thinking of them in the first place ***(Levy, 1998).***

Newborn screening was one of the first and largest population based disease intervention program, these programs were initially designed to detect infants with possible inborn errors of metabolism. If screening is positive or results are unusual, additional testing is performed to confirm the diagnosis. After the diagnosis is confirmed medical interventions are initiated. Infants and children are then followed over time to confirm effectiveness of treatment. Lifelong services are essential to those infants and their families ***(Pass et al., 2000).***

Early clinical signs of metabolic disorders are non specific and difficult to distinguish in infants. Some disorders are asymptomatic in the neonatal period and present later in life. These diseases mimic many other conditions; often the health care provider may not immediately identify them as the underlying etiology. In

some disorders there are no early symptoms at all ***(Banta-Wright & Steiner, 2003).***

Except for hearing screening, all newborn screening tests are done using few drops of blood through pricking baby's heel. The same blood sample can be used to screen for 55 or more disorders. A blood specimen should be taken from every newborn before hospital release, usually at 24 to 48 hours of life. The American Academy of Pediatrics recommended that a repeat specimen be taken one to two weeks later. Babies born outside the hospital should have newborn screening tests done before the seventh day of life ***(American Academy of Pediatrics, 2003).***

Recent scientific and technological advances are making pressure to expand the scope of newborn screening programs. The ability to examine DNA in the Guthrie specimen has opened up opportunities to screen for many disorders that previously were difficult to identify in the newborn, but these proposals also challenge our current perception of newborn screening programs ***(Levy, 2003).***

AIM OF THE WORK:

To discuss in details the various methods used for neonatal screening and its importance in catching the affected newborns and beginning the treatment before symptoms occur.

NEONATAL SCREENING

Newborn screening is a wonderful example of preventive medicine pioneered by Dr. Robert Guthrie in the early 1960s. The blood testing of newborn for treatable disorders has become almost universal in developed countries ***(Wilcken, 2003).***

This screening is intended to detect disorders that can result in early mortality or lifelong disability ***(Chace et al., 1999).***

Although the incidence of each specific disorder is rare, their collective importance is deemed to be of considerable public health significance ***(Pandor et al., 2004).***

Today, newborn screening programs provide services for detecting a variety of disorders that are amenable to pediatric clinical interventions established by specialists in biochemical genetics, endocrinology hematology, infectious disease or pulmonology ***(Mandle, 2002).***

National Standards for Newborn Screening:

Screening newborn babies should fulfill the modified Wilson criteria:

- Clinically and biochemically well defined disorder.
- Known incidence in population

- Disorder associated with significant morbidity or mortality
- Available effective treatment
- Period before onset during which intervention improves outcome
- Ethical, safe and simple screening test
- Cost effectiveness of screening ***(Seymour et al., 1997).***

HISTORY OF NEONATAL SCREENING

Dr. Robert Guthrie developed the first simple, sensitive, and inexpensive screening test for hyperphenylalanemia in 1962 ***(Pass et al., 2000).***

With this test phenylalanine, in blood dried on filter paper, inhibits bacterial growth ***(Brewer et al., 2000).***

Prior to the Guthrie assay, a ferric chloride test was used to detect phenylalanine on wet diapers ***(Pass et al., 2000).***

Infants identified as having hyperphenylalanemia were treated with a low-phenylalanine diet. Dr. Guthrie discovered that with early identification and treatment, infants had normal cognitive development compared to untreated infants who developed severe mental retardation. ***(Brewer et al., 2000).***

In the mid of 1960s, soon after this discovery, implementation the 1st universal newborn screening program, which at the time screened for only one disorder, hyperphenylalanemia ***(Millington, 2003).***

Soon newborn hyperphenylalanemia screening became available nationwide. Since then, technological advancements have led to an improvement in the number of disorders screened ***(Millington, 2003).***

Screening for several metabolic disease, including galactosemia, Maple syrup urine disease and homocystinuria, was initiated by the late 1960s. In 1970s, screening and early treatment for congenital hypothyroidism was adopted to prevent intellectual disabilities. A few tests, including tests for adenosine deaminase deficiency and α-1-antitrypsin deficiency were introduced in the 1970s but subsequently removed because clinical benefits were not apparent ***(Brewer et al., 2000).***

Newborn screening for sickle cell disease (SCD) and other hemoglobinopathies was introduced in 1970s but did not become widely adopted until after 1987. The recommendation for screening was based on evidence from a clinical trial that showed that antibiotic prophylaxis begun before 6 months of age could prevent most cases of pneumococcal sepsis in children with sickle cell anemia ***(Brewer et al., 2000).***

TANDEM MASS SPECTROMETRY

Mass spectrometry is an analytical technique that is used to identify unknown compounds, quantify known materials, and elucidate the structural and physical properties of ions. A mass spectrometer is a device that separates and quantifies ions based on their mass to charge ratios (Fig. 1). Mass spectrometers measure weight (i.e. mass) electronically and display results in the form of mass spectrum. A mass spectrum is a graph that shows each specific molecule by weight and how much of each molecule is present. Tandem mass spectrometry, (MS/MS) is based on the use of two mass spectrometers connected in series by a chamber (known as a collision cell), which breaks down molecules into their constituent pieces. A sample is sorted and weighed in the first mass spectrometer, and fragmented within the collision cell, and then the pieces are further sorted and weighed in the second spectrometer ***(Pandor et al., 2004).***

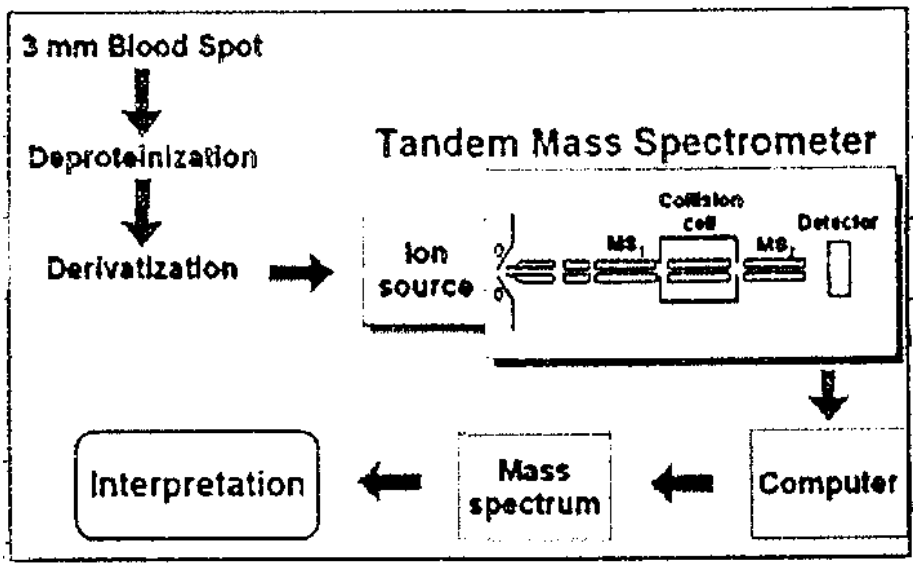

Figure (1): *Basic scheme of an MS/MS analysis (Pandor et al., 2004).*

Schematic representation of a tandem mass spectrometer: Ions formed in the ion source are transferred to MS1, filtered and passed on to the collision cell where they are accelerated and collide with an inert gas. The product ions are filtered by MS2 before being passed to the detector ***(Pandor et al., 2004).***

Different types of mass spectrometer are available. One distinguishing feature of a MS/MS system is the way in which the compound is placed into the tandem MS [e.g. fast atom bombardment, liquid secondary ion, electrospray ionisation (ESI)]. The preferred type of sample introduction is by electrospray ionisation, as this allows a continuous flow approach. Therefore a single tandem mass instrument can process a large volume of specimens, through the use of an automated sampler ***(Pandor et al., 2004).***