NEWBORN SCREENING

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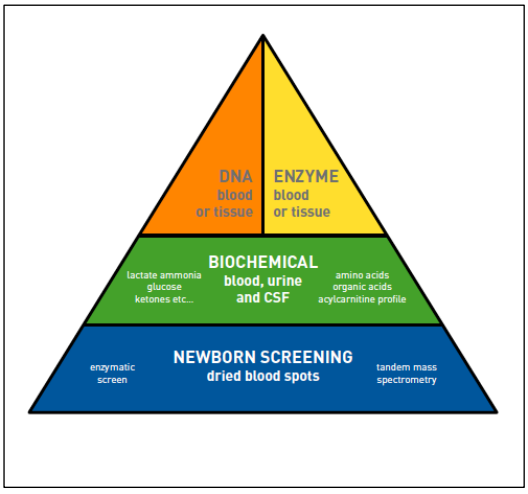
NEWBORN SCREENING

- It is a public health service
- It is the practice of testing all babies for certain disorders and conditions that can hinder their normal development such as rare genetic, hormone-related and metabolic conditions that can cause serious health problems.
- Early identification is important since timely intervention leads to significant reduction of morbidity, mortality and associated disabilities
- Newborn Screening Act of 2004 is also known as Republic Act 9288
    - Goal: provide an opportunity for every newborn for early identification of conditions that can cause mental retardation or death
- We screen for disorders that are present in our population. Take note that different countries will have a different set of disorders that they screen for.
- When screening for disorders, the following must be taken into consideration:
    - There is benefit to the individual from early diagnosis
    - The benefit is reasonably balanced against financial and other costs
    - There is a reliable test suitable for newborn screening
    - There is a satisfactory system in operation to deal with diagnostic testing, counseling, treatment and follow-up on patients identified by the test
- Most of the disorders included in the ENBS are inherited via an autosomal recessive manner
- G6PD Deficiency is the only condition included in ENBS that is inherited in an X-linked recessive manner which explains why more males are affected compared to females

- Newborn screening is a process of filtration
- Newborn screening is NOT diagnostic
- Confirmatory tests include:
    - Biochemical tests – blood, urine
    - DNA testing
    - Enzyme analysis



- Majority of the disorders included in the panel are metabolic disorders. IEMs are disorders caused by a deficiency of enzyme catalysis or an enzyme that facilitates the transport of biological substances across membranes

- The principles of treatment will address the pathophysiology of the disorder. Substrate reduction through diet, provision of co-factor or enzyme and supplying the missing product. In addition, the excretion of toxins should be facilitated either through medical means or via dialysis.
- For most IEMs in the ENBS panel, while awaiting results, patients are encouraged to continue breastfeeding as breast milk has low protein (1 ml = 0.01g of protein).

- The only condition included in the ENBS for which breastfeeding is absolutely contraindicated is galactosemia. Galactosemia is a disorder where lactose cannot be effectively broken down.
- Principles of Treatment during Acute Crisis
    - Address the precipitating factor which caused the catabolic state
    - Reverse the catabolic state by administration of high-energy intake
    - Reduce toxin production by reduction or omission of natural protein
    - Amplify physiological detoxifying mechanisms
    - Provide deficient metabolites (if applicable)
- Principles when well
    - Provide adequate calories and nutrients for growth and development
    - Maintain normal to acceptable monitoring levels
- Long-Term Treatment
    - Prevention of death or permanent brain injury during acute metabolic crises
    - Normal growth and development
    - Normal monitoring levels
- Prognostic Factors
    - Age of diagnosis
    - Degree of illness during diagnosis
    - Dietary control when well
    - Control of catabolism during illness
    - Access to acute medical care
- Disorders included in the ENBS panel

Collection of samples should be done immediately after 24 hours from birth
PT (<37 wks) and LBW (<2000g) should repeat samples at 28th DOL.

Disorder	Enzyme Defect	Outcome if Not Treated
Congenital Hypothyroidism	Multiple disorders	Large fontanelles, jaundice, macroglossia, hypotonic, leathargic, weak cry
Congenital Adrenal Hyperplasia	21-hydroxylase deficiency	Ambiguous genitalia Death Salt wasting Simple virilizing
Phenylketonuria	Phenylalanine hydroxylase PTPS deficiency	Neurological problems Mental retardation
Galactosemia	Galactose 1 phosphate uridyl transferase Galactokinase Galactose-4-epimerase	Jaundice, feeding intolerance, FTT, hepatomegaly Cataracts
Glucose-6-Phosphate Dehydrogenase Deficiency	Glucose-6-Phosphate Dehydrogenase	Jaundice Pallor
Maple Syrup Urine Disease	Branched chain ketoacid dehydrogenase enzyme	Seizures Maple syrup odor in cerumen and urine Coma and respiratory failure

Disorder	Deficient Enzyme	Outcome if Not Treated
Tyrosinemia Type I (TYR)	Fumarylacetoacetate hydrolase	Acute hepatic failure, coagulopathy, and/or renal tubular dysfunction, growth failure
Homocystinuria (HCY)	Cystathione-B-synthetase	Thromboembolism, Marfan-like phenotype, dislocated lens, developmental delay
Methionine adnosyltransferate deficiency (MAT)	Methinone adenosyltransferase	Cerebral edema and demyelination
Citrullinemia Type I (CIT)	Argininosuccinate synthetase	Lethargy, vomiting, seizures, hepatomegaly, retardation
Argininosuccinic Aciduria (ASA)	Argininosuccinate lyase	Lethargy, vomiting, seizures, hepatomegaly, retardation

Disorder	Deficient Enzyme	Outcome if Not Treated
Propionic Acidemia (PA)	Propionyl-CoA Carboxylase	Vomiting, ketosis, death, mental retardation
Isovaleric Acidemia (IVA)	Isovaleryl-CoA Dehydrogenase	Failure to thrive, developmental delay
Methylmalonic Acidemia (MMA)	Methylmalonyl-CoA Mutase	Tubulointerstitial nephritis with progressive renal failure
3-Methylcrotonyl CoA Carboxylase Deficiency (3-MCC)	3-Methylcrotonyl CoA Carboxylase	Failure to thrive, hypotonia, cardiomyopathy
Biotinidase	Biotinidase	Hypotonia, ataxia, seizures, hearing loss, visual loss, eczema, alopecia
Holocarboxylase Synthetase Deficiency	Holocarboxylase Synthetase	Hypotonia, ataxia, seizures, hearing loss, visual loss, eczema, alopecia, death
Glutaric Acidemia Type I (GA I)	Glutaryl CoA Dehydrogenase	Macrocephaly, encephalopathic episodes with basal ganglia stroke, hypotonia, dyskinesia
Beta-Ketothiolase Deficiency	Mitochondrial Acetoacetyl-CoA Thiolase	Progressive loss of mental and motor skills, hypotonia, lethargy, coma, hyperventilation

Disorder	Deficient Enzyme	Outcome if Not Treated
Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)	Medium Chain Acyl-CoA Dehydrogenase	Hypoglycemia, Failure to thrive, developmental delay, sudden infant death syndrome
Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)	Very Long Chain Acyl-CoA Dehydrogenase	Hypoglycemia, muscle pain, myoglobinuria, sudden infant death syndrome
Carnitine Uptake Defect (CUD)	Carnitine Transporter Defect	Cardiomyopathy, sudden infant death syndrome
Carnitine Palmitoyltransferase Type I Deficiency (CPT I)	Carnitine Palmitoyltransferase Type I	Hypoglycemia, convulsions, coma
Carnitine Palmitoyltransferase Type II Deficiency (CPT II)	Carnitine Palmitoyltransferase Type II	Hypoglycemia, convulsions, coma
Long chain Hydroxyacyl CoA Dehydrogenase Deficiency (LCHAD)	Long Chain Hydroxyacyl CoA Dehydrogenase	Skeletal myopathy, peripheral neuropathy
Trifunctional Protein Deficiency (TFP)	LCHAD, Long Chain 2,3 Enoyl CoA Drasate and LKAT	Fatal arrhythmia, muscle pain and weakness
Multiple Acyl-CoA Dehydrogenase Deficiency (MAD or GA II)	Electron Transport Flavoprotein and ETF-Ubiquinone Oxidoreductase	Hypoglycemia, death

Cystic Fibrosis	• Due to abnormalities of CF transmambrane conductance regulator (CFTR) protein • **SSx:** intestinal blockage, failure to thrive, chronic respiratory symptoms, hypoelcetrolytemia from sweat salt loss, malnutrition, pancreatic insufficiency • **Tx:** pancreatic enzyme, fat-soluble vitamins, salt supplementation
Hemoglobinopathies	• Loss of one alpha gene results in a silent carrier state (no anemia or microcytosis) • Loss of two genes results in alpha thalassemia trait (mild anemia and microcytosis) • Loss of three genes HbH disease (hemolytic anemia) • Loss of all four genes Hb Barts (hydrops fetalis and in utero death) • **Tx:** folate supplementation, intermittent transfusion, BMT

Category – Definition, Biochemistry, Genetics	Key Characteristics and Examples
Aminoacidopathies	
Involves abnormal levels of amino acids with the amino group still attached; includes primary catalytic defects, cofactor defects, transporter defects Almost all are autosomal recessive	Usually not acidotic (except MSUD or with the renal tybylar acidosis of tyrosinemia). Typically but not always affects CNS (eg. PKU, glycine encephalopathy), may affect other organs (eg., liver and renal tubules in tyrosinemia type 1). Episodic, static or progressive. Homocystinuria may present with stroke or clotting, with or without intellectual disability. Diagnosis with PAA, sometimes UAA, sometimes confirm by enzyme assay and/or DNA. Special presentation – when the mother has PKU or hyperphenylalaninemia, she may be normal and unaware of diagnosis but have babies with microcephaly and intellectual disability; this has nearly 100% recurrence risk and adverse outcome is preventable with treatment of mother; diagnose it by plasma amino acids in mother
Organic Acidemias	
Involves metabolites of amino acids after amino groups removed and other compounds with C, H and O (fatty acids and lactate/energy in separate categories). Essentially all are autosomal recessive	Usually but not always acidotic, anorexia/vomiting; episodic altered consciousness; may include bone marrow depression or other end-organ failure. Diagnosis with urine organic acids; blood acylcarnitine profile may be helpful, enzyme assays or DNA for confirmation when available
Urea Cycle Defects	
Involves the urea cycle, typically with altered levels of the amino acids in the urea cycle. Most are autosomal recessive but the most common is X-linked	Altered mental status, decreased appetite or intractable or recurrent emesis including “cyclical vomiting”, migraine, ataxia and often with protein aversion. Typically not acidotic unless in shock; respiratory alkalosis is common. Diagnosis by PAA, in some cases confirmed with enzyme assays and/or DNA.
Fatty Acid Oxidation and Carnitine Metabolism Disorders	
Involves the oxidation of fatty acids to ketones and the transport of fatty acids into the mitochondrion for oxidation. Essentially all are autosomal recessive	Classic presentation is Reye syndrome or SIDS in an infant or toddler, but more commonly the presentation is excessive irritability or lethargy with ordinary childhood illness or extended fasting. The hallmark is hypoketosis, but some ketones are usually present, and hypoglycemia is only sometimes present. Also may present with liver failure, FTT, cardiomyopathy, and/or rhabdomyolysis; retinopathy and bone marrow failure may occur. Diagnose with acylcarnitine profile, but that may be normal when well, and diagnose some conditions with carnitine levels. Some diagnosis may be confirmed with enzyme assays and/or DNA
Carbohydrate Disorders	
Involving metabolism of sugars (with glycogen storage disorders separated out); examples are galactosemia and the disorders of fructose metabolism. Essentially all are autosomal recessive	Typically presenting with liver disease and/or hypoglycemia and acidosis, often with renal tubular disease. Cataracts may be seen in galactosemia at presentation in some cases and develop in untreated cases. Diagnosis based on enzyme assay or DNA.

Biotin Responsive Disorders

- What are biotin responsive disorders?
  - Due to defects in recycling of biotin or lack of biotin
- Symptoms
  - Metabolic ketoacidosis, organic aciduria, mild hyperammonemia
  - Seizures, hypotonia, ataxia, developmental delay, vision problems, hearing loss, cutaneous abnormalities
- Treatment
  - Biotin supplementation

Additional resources to access:
newbornscreening.ph – Look at the resources part and you can see the different AOs/memos on NBS and the fact sheets for doctors
https://www.youtube.com/watch?v=_UFAAF4cZ2o – video on NBS

References

1. Padilla CD and BL Therrell. Newborn Screening in the Asia Pacific Region. J Inherit Metab Dis 2007;30:490-506
2. American Academy of Pediatrics, Saul RA (ed.), Medical Genetics in Pediatic Practice, 1st ed. AAP, 2013
3. Clarke JTR, A Clinical Guide to Metabolic Diseases, 3rd ed., 2005
4. Carroll and Rideout Lecture, 2010 https://www.mountsinai.on.ca Accessed 17 March 2017
5. https://ghr.nlm.nih.gov/primer/newbornscreening/nbs Accessed 29 January 2020
6. https://www.vitaflo-via.com/disorder-resources/rare-disorders-protein-metabolism/adapting-clinical-iem-services-meet-modern Accessed 29 January 2020
7. Camp KM, Lloyd-Puryear MA and Huntington KL. Nutritional Treatment for inborn errors of metabolism: indications, regulations, and availability of medical foods and dietary supplements using phenylketonuria as an example. Mol Gen Metab 2012;107(1-2):3-9
8. Leao LL and Burle de Aguiar MJ. Newborn screening: what pediatricians should know. J Pediatr (Rio J) 2008;84(4 Suppl):S80-90
9. Morton DH, Strauss KA, Robinson DL, Puffenberger EG and Kelley RI. Diagnosis and treatment of maple syrup urine disease: a study of 36 patients. Pediatrics 2002;109(6):999-1011