Abnormal Newborn Screening – What To Do Next? An Approach to Metabolic Disorders

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Objectives

- Recognize and understand the role of Newborn Screening in Metabolic Disorder
- Review past, present and future of Newborn Screening
- Discuss clinical approach to Metabolic Disorders and identify management strategies.
- Understand the role of provider and caregiver in the management of common childhood illnesses in children with specific Metabolic Disorders.
Case 1

NF, a 4 day old full-term boy, born via SVD, had normal newborn resuscitation and course, discharged home on day 2 of life, referred to UKCH for a abnormal newborn screen over a weekend.
Hospital Course and Outcome

On admission –
CC: by mother ‘something wrong with the PKU test’, ‘not waking up for feeds easily’ and ‘seems tired during breastfeeding’

PE: small {wt. 1.9kg (birth wt -2.2kg)}, jaundice, not active.


Acute rapid intervention with IVF, close IP monitoring, confirmatory testing – MCADD, on metabolic management....

Outcome - a healthy ~ 3 yrs old toddler, who loves to go fishing & hunting with his dad.
# Newborn Screening History

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1934</td>
<td>Dr. Asbjörn Fölling, Norway discovered ‘imbecillitas phenylpyruvica’ later renamed as Phenylketonuria or PKU.</td>
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<tr>
<td>1951</td>
<td>Dr. Horst Bickel, Germany discovered dietary treatment by producing low Phenylalanine formula.</td>
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<tr>
<td>1957</td>
<td>Dr. Willard Centerwall, California discovered the first diagnostic testing in urine by detecting phenylpyruvic acid – diaper test → used for mass screening.</td>
</tr>
<tr>
<td>Year</td>
<td>Event</td>
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<tr>
<td>------</td>
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<tr>
<td>1961</td>
<td>Dr. Robert Guthrie developed dried blood on filter paper test to detect Phenylalanine soon after birth; enabling infants to be on a special diet before any brain damage could occur.</td>
</tr>
<tr>
<td>1962</td>
<td>Dr. George Jervis of New York discovered that enzyme defect resulting in inability to breakdown Phenylalanine in liver leads to the disorder.</td>
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<tr>
<td>Year</td>
<td>Event</td>
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<td>------</td>
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<tr>
<td>1962</td>
<td>President Kennedy presents International Kennedy Award to Dr. Fölling.</td>
</tr>
<tr>
<td>1962</td>
<td>Dr. Robert Guthrie and Dr. Robert MacCready in Massachusetts tested every newborn for PKU.</td>
</tr>
<tr>
<td>1963</td>
<td>Massachusetts became the first state to mandate newborn screening for PKU.</td>
</tr>
<tr>
<td>1966</td>
<td>Majority states mandated screening for PKU and today all of them do.</td>
</tr>
</tbody>
</table>
Different States screening mandate varied widely......

some were screening for as few as 3 disorders; while others as many as 43
Newborn Screening Advocacy – AAP role

1999

AAP Newborn Screening Task Force recommended that “HRSA should engage in a national process involving government, professionals, and consumers to advance the recommendations of this Task Force and assist in the development and implementation of nationally recognized newborn screening system standards and policies.”
2002 The Maternal and Child Health Bureau (MCHB) of HRSA commissioned the American College of Medical Genetics (ACMG) to:

- outline a process of standardization of outcomes and guidelines for State newborn screening programs;
- define responsibilities for collecting and evaluating outcome data;
- recommended uniform panel of conditions to include in State newborn screening programs.
Expanded Newborn Screening

2004 ACMG prelim report strongly advocated by March of Dimes for policy implementation at Federal and State levels.

Jan. 2005 29 core disorders identified and recommended (G6PD dropped).

May 2006 ACMG report - ‘Newborn Screening: Toward a Uniform Screening Panel and System.’
Kentucky Newborn Screening History
(thanks to Dr. C. Charlton Mabry)

<table>
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<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1962</td>
<td>Voluntary urine screening in KY for PKU</td>
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<tr>
<td>1966</td>
<td>KY House Bill 164 effective 7/11/66 begins PKU screening</td>
</tr>
<tr>
<td>1980</td>
<td>Addition of testing for Galactosemia and Congenital Hypothyroidism</td>
</tr>
<tr>
<td>1995</td>
<td>Addition of Sickle cell /Hemoglobinopathy screening</td>
</tr>
<tr>
<td>2005</td>
<td>KY Senate Bill 64 effective 12/5/2005 begins Expanded Newborn Screening</td>
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</table>
National Trend in Newborn Screening

- Newborn Screening - a 10 year journey as it evolves ..... 

- state of the States through time
U.S. Newborn Screening
Mandated Disorders – October 2000
(Note: Other disorders may be offered but are not mandated)

More than 8 Disorders (8)
8 Disorders (3)
7 Disorders (5)
6 Disorders (8)
5 Disorders (10)
4 Disorders (14)
3 Disorders (3)
U.S. Newborn Screening
Conditions Required – February 1, 2009
(Conditions available as an option to a selected population are not counted – Must be universally required)
The Newborn Screening Saves Lives Act (H.R. 3825, S. 1858)

- Introduced in the Senate by Sen. Chris Dodd [CT] in July 23, 2007 (21 co-sponsors) as S. 1858


President signs it into Public Law 110-204 on April 24, 2008
Future.....

• Newer disorders being considered (LSD, SCID, α -1 antitrypsin, Fragile X, peroxisomal d/o)

• Newer technology being discussed (Next Generation Sequencers, digital microfluidics, CGH array)

• Newer disorders added by individual States (KY tests for 15 additional d/o since Sept. 2008)
1. Does screening improve outcomes for the infant or family?

2. Is there a screening test or screening test algorithm for the condition with sufficient analytic validity?

3. Has the clinical validity of the screening test or screening algorithm, in combination with the diagnostic test or test algorithm, been determined and is that validity adequate?
4. Is there a case definition that can be uniformly and reliably applied? What are the clinical history and spectrum of disease of the condition, including the impact of recognition and treatment?

5. What is the clinical utility of the screening test or screening algorithm?
   - 5a: What are the benefits associated with use of the screening test?
   - 5b: What are the harms associated with screening, diagnosis and treatment?
NBS Specimen Collection Nuances
NBS Specimen collection facts

- <24h valid for GAL, Hemoglobinopathy, BIOT
- 24-72 ideal - valid for above and AA, OA, FAO d/o
- KY NBS good through first 6 months of life for repeat
Kentucky Expanded Newborn Screening

5 categories:
- Amino acid metabolism disorders
- Organic acid metabolism disorders
- Fatty acid oxidation disorders
- Hemoglobinopathies
- Others
### Amino Acid metabolism disorders* (MS/MS)

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tbody>
<tr>
<td><strong>PKU</strong></td>
<td>Phenylketonuria</td>
</tr>
<tr>
<td><strong>MSUD</strong></td>
<td>Maple syrup urine disease</td>
</tr>
<tr>
<td><strong>HCY</strong></td>
<td>Homocystinuria</td>
</tr>
<tr>
<td><strong>CIT</strong></td>
<td>Citrullinemia</td>
</tr>
<tr>
<td><strong>ASA</strong></td>
<td>Argininosuccinic acidemia</td>
</tr>
<tr>
<td><strong>TYR I</strong></td>
<td>Tyrosinemia type I</td>
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</tbody>
</table>
**Organic Acid metabolism disorders***(MS/MS)**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>IVA</td>
<td>Isovaleric Acidemia</td>
</tr>
<tr>
<td>GA-I</td>
<td>Glutaric Acidemia type I</td>
</tr>
<tr>
<td>HMG</td>
<td>Hydroxymethylglutaric Aciduria or HMG-CoA lyase deficiency</td>
</tr>
<tr>
<td>MCD</td>
<td>Multiple Carboxylase deficiency</td>
</tr>
<tr>
<td>MUT</td>
<td>Methylmalonic Acidemia due to mutase deficiency</td>
</tr>
<tr>
<td>Cbl A,B</td>
<td>Methylmalonic acidemia cblA and cblB forms</td>
</tr>
<tr>
<td>3MCC</td>
<td>3-Methylcrotonyl-CoA Carboxylase deficiency</td>
</tr>
<tr>
<td>PROP</td>
<td>Propionic Acidemia</td>
</tr>
<tr>
<td>BKT</td>
<td>Beta-Ketothiolase deficiency</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>SCAD</td>
<td>Short Chain Acyl-CoA Dehydrogenase deficiency (KY NBS)</td>
</tr>
<tr>
<td>MCAD</td>
<td>Medium Chain Acyl-CoA Dehydrogenase deficiency</td>
</tr>
<tr>
<td>VLCAD</td>
<td>Very Long Chain Acyl-CoA Dehydrogenase deficiency</td>
</tr>
<tr>
<td>LCHAD</td>
<td>Long-chain 3-OH Acyl-CoA Dehydrogenase deficiency</td>
</tr>
<tr>
<td>TFP</td>
<td>Trifunctional Protein deficiency</td>
</tr>
<tr>
<td>CUD</td>
<td>Carnitine Uptake Defect</td>
</tr>
</tbody>
</table>
Hemoglobinopathies (HPLC)

- **Hb SS** - Sickle cell anemia
- **Hb S/Th** - Hb S/Beta-Thalassemia
- **Hb S/C** - Hb S/C disease
• **CH** - Congenital Hypothyroidism (*T₄*, *TSH* assay)
• **CAH** - Congenital Adrenal Hyperplasia (fluoroimmunoassay)
• **BIOT** *-* Biotinidase deficiency (time sequence colorimetry)
• **GALT** *-* Classical Galactosemia (fluorometric NADPH determination)
• **HEAR** - Hearing loss (*OAE /BAER*)
• **CF** - Cystic Fibrosis (*IRT* Assay)

*disorders seen in the UK Metabolic Clinic*
UK / KY East catchment for KY NBS (in blue)

Kentucky - Health Services
- Area West
- Area East
3 year UK/KY East Newborn Screening Experience
Referrals (744)/Confirmed cases (195)

Galactosemia
Biotinidase deficiency
Organic acidemias
Fatty acid oxidation disorders
PKU & other aminoacidopathies
Hemoglobinopathies
Cystic Fibrosis
Congenital adrenal hyperplasia
Congenital hypothyroidism

Confirmed Cases
Referred Cases
KY East Expanded Newborn Screening Confirmed Cases (195)
3 years experience

- Congenital hypothyroidism, n = 42
- Congenital adrenal hyperplasia, n = 0
- Cystic Fibrosis, n = 23
- Hemoglobinopathies, n = 4
- PKU & other aminoacidopathies, n = 7
- Fatty acid oxidation disorders, n = 28
- Organic acidemias, n = 3
- Biotinidase deficiency, n = 49
- Galactosemia, n = 39
What are the implications?

- Changing Prevalence and Incidence data for these disorders

- More and more abnormal screen reports will be made available to PCP; warranting acute visits, basic evaluation and management +/- counseling

- More of these children will present to ED and will need prompt and timely care; even if presenting symptoms or complains of common childhood illnesses
What are the implications?

- More of these children will be admitted for observation during common illnesses to avert metabolic crisis.

- Surgical procedure/ Anesthesia requiring fasting need to be considered carefully.

- Quality of life through infancy, toddler, and school years, and transition into adulthood as we take care of emerging newer types of chronic diseases.

- New knowledge of clinical spectrum and outcomes.
Approach to Inborn Errors of Metabolism........which path(way) to take???????
It’s only that simple ...............
Approach to IEM dependent on...

- Clinician’s first consideration of presentation
- Family History
- Prenatal history
- Consanguinity
- Appropriate lab tests availability and specimen collection expertise
- Newborn Screen Report; if available
When to think about IEM etiology?

Apart from abnormal Newborn Screen or at-risk families; clinical presentation in...........

- Early symptoms in antenatal and neonatal period [<1yr age]
- Later onset acute and recurrent attacks of symptoms [late infancy and beyond]
- Chronic and Progressive generalized symptoms [early and late childhood]
- Specific and permanent organ presentation
Early acute non specific symptoms in antenatal and neonatal period

- **Microcephaly** – maternal PKU
- **Predominant seizures** – NKH, MCD, GLUT1,
- **Neurological deterioration** – UCD, MSUD, MMA, PA, IVA, MCD
- **Jaundice/ liver failure** – GALT, HFI, LCHAD, CDG
- **Cardiac Failure/ Rhythm abnormality** – FAOD, ETC, Pompe
- **Persistent hypoglycemia** – FAOD, PHHI
Later onset acute and recurrent attacks of symptoms [late infancy and beyond]

- Rapid course → spontaneous improvement/ death
- Normal in-between attacks
- Precipitated by inter-current events

- Acute Encephalopathy - coma, strokes, seizures, vomiting + lethargy
- Ataxia
- Psychiatric symptoms – agitation, schizophrenia, psychosis
- Dehydration
- ? SIDS
### Chronic & Progressive general symptoms

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G I</td>
<td>anorexia/feeding difficulties, FTT, chronic vomiting, chronic diarrhea</td>
</tr>
<tr>
<td>Muscle</td>
<td>hypotonia, poor muscle mass, myopathy, idiopathic non obstructive</td>
</tr>
<tr>
<td></td>
<td>cardiomyopathy</td>
</tr>
<tr>
<td>Neurodev</td>
<td>early nonspecific progressive developmental delay, seizures, hypotonia,</td>
</tr>
<tr>
<td></td>
<td>ataxia, autistic features, macrocephaly, irritability, myoclonus,</td>
</tr>
<tr>
<td></td>
<td>polyneuropathy, behavioral</td>
</tr>
</tbody>
</table>
What lab tests and when?

**Common (2-4hrs)**

- CBC (pancytopenia, leukopenia)
- BMP/CMP (hypoglycemia, metabolic alkalosis, metabolic acidosis, LFT)
- UA – odor, ketones, reducing substance
- Ammonia (50-100, >100) *
- Lactate (> 4)*
- Pyruvate
- Lactate/Pyruvate ratio (< 20, > 20) – plasma and CSF

**Specialized Biochemical (1-2 weeks)**

- Plasma and Urine Carnitine Panel
- Plasma Acylcarnitine
- Urine Organic Acid Profile/ Acylglycine Profile
- Plasma, CSF and Urine Amino Acids

**Enzyme Assays and DNA Mutation analysis (> 2-4 weeks)**
Metabolic Acidosis
(pH < 7.30, pCO2 < 30, HCO3- < 15)

Anion Gap
[Na+ - (Cl- + HCO3-) + fixed acids/ions such as proteins, organic acids, sulfate, phosphate and lactic acid]

Normal (8-12mEq/L)

Renal Loss HCO3-/Intestinal Loss HCO3

High

Accumulation of fixed acids

Ketosis/Ketonuria

Hyperglycemia
Normoglycemia
Hypoglycemia

Ammonia
Lactate
Lactate

High (50-100)
Normal
High
Normal

Diabetes
Ketolytic Defect
OA
MSUD

Mitochondrial d/o
Respiratory Chain d/o (L/P RATIO >20)
Gluconeogenesis d/o

No Ketosis/Ketonuria

High Lactate
Normal Lactate

Hypoglycemia
Normoglycemia
Normoglycemia

FAOD (abnl UOA)
GSD1
PDH def-cy (L/P ratio <20)
Pyroglutamic aciduria

OA
MSUD
OA

Adrenal insufficiency
Fructosemia
Endogenous production → SUBSTRATE → Removal
Diet
Treatment / Management Principles

During acute crisis –

- Eliminate any oral/parenteral source
- Prevent catabolism/stimulate anabolism
- Improve hydration
- Continue other cardiovascular and respiratory critical care support
- ‘Cleansing’ Medications or hemodialysis to remove accumulated metabolites
During acute crisis

- Administer a simple source of calorie enough to suppress any tissue catabolism and mobilization of the endogenous source
  
  ✓ 100-110 cal/kg/day
  
  ✓ $D_{10}W$ or higher + electrolytes @ min. 1 ½ M
  
  ✓ L – carnitine, Glycine for OA/FAOD
  
  ✓ Sodium benzoate, Sodium phenylacetate, Arginine, Citrulline for UCD
Nutrition Support Strategies in chronic management of metabolic disorders

- Reduce intake of any precursor metabolites that accumulate as a result of the missing or inactive enzyme
- Utilize alternative pathways
- Replacing any deficiencies that develop as a result of the missing or inactive enzyme
Management Principles for core NBS d/o

- **Phenylketonuria (PKU) and other Aminoacidopathies** – dietary restriction of offending protein/ amino acid with medical food supplementation, cofactor replacement

- **Organic Acidemia** – dietary protein restriction with medical food and vitamin supplementation
Management Principles for core NBS d/o

• **Fatty Acid Oxidation Disorder** – Avoid fasting and dietary fat restriction with essential fatty acid supplementation

• **Galactosemia** – Dietary restriction of lactose

• **Biotinidase Deficiency** – Vitamin supplementation
Role of all involved in IEM

- Parents/ Guardian
- Primary Care Provider / Sub specialist
- Clinic / Hospital Support staff / Nurses / Lab Technologist / Dietitian / Pharmacy
- ED / In patient services
- Surgery / Anesthesia / Critical Care
- Advocates – Individual / Collective
- Educators (undergrad, med, grad, post grad)
- Policy maker / Administrator – Hospital / State / Federal
References

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- KY Newborn Screening Program
  chfs.ky.gov/dph/ach/ecd/newbornscreening.htm
- Book ‘Robert Guthrie - the PKU Story: Crusade Against Mental Retardation’ by Jean Koch
- March of Dimes www.marchofdimes.com
- Wyllie et al, Pediatric GI and Liver Disease, 2006
ONE DAY ALL BABIES WILL BE BORN HEALTHY
WE NEED TO WALK TO GET THERE

Join the thousands of people already involved in your community.