Abnormal Newborn Screening - Metabolic disorders

Shibani Kanungo, MD, MPH, FAAP
Assistant Professor,
Department of Pediatrics and Health Behavior,
University of Kentucky College of Medicine and Public Health

Family Medicine Review
May 11th, 2010
November 27th, 2009

Objectives

• Discuss Metabolic Disorders in Newborn Screening

• Recognize and understand the role of Newborn Screening Technique in Metabolic Disorder identification

• Discuss clinical approach and management strategies on Abnormal Newborn Screening for Metabolic Disorders.

• 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 an abnormal newborn screen over a weekend.
Until 2009 screening mandate varied widely in different States ..... some were screening for as few as 3 disorders; while others as many as 43
Slide 7

Slide 8

Slide 9

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 6months of life for repeat
Slide 10

Expanded Newborn Screening

5 categories:
- Amino Acid Disorders *
- Organic Acid Disorders *
- Fatty Acid Oxidation Disorders *
- Hemoglobinopathies
- Others * (Galactosemia, Biotinidase Deficiency)

* disorders seen in the UK Pediatric Metabolic Clinic

Slide 11

Amino Acid metabolism disorders* (MS/MS)

- PKU - Phenylketonuria
- MSUD - Maple syrup urine disease
- HCY - Homocystinuria
- CIT - Citrullinemia
- ASA - Argininosuccinic acidemia
- TYR I - Tyrosinemia type I

Slide 12

Organic Acid disorders* (MS/MS)

- IVA - Isovaleric Acidemia
- GA I - Glutaric Acidemia type I
- HMG - Hydroxymethylglutaryl-CoA or HMG-CoA lyase deficiency
- MCD - Multiple Carnitine deficiency
- MUT - Methylmalonic Acidemia due to mutase deficiency
- Cbl A,B - Methylmalonic acidemia cblA and cblB forms
- 3MCC - 3-Methylcrotonyl-CoA Carboxylase deficiency
- PROP - Propionic Acidemia
- BKT - Beta-Ketothiolase deficiency
Fatty Acid Oxidation disorders* (MS/MS)

- **SCAD** - Short Chain Acyl-CoA Dehydrogenase deficiency (KS-SD)
- **MCAD** - Medium Chain Acyl-CoA Dehydrogenase deficiency
- **VLCAD** - Very Long Chain Acyl-CoA Dehydrogenase deficiency
- **LCHAD** - Long-chain 3-OH Acyl-CoA Dehydrogenase deficiency
- **TFP** - Trifunctional Protein deficiency
- **CUD** - Carnitine Uptake Defect

Hemoglobinopathies (HPLC)

- **Hb SS** - Sickle cell anemia
- **Hb S/Th** - Hb S/Beta-Thalassemia
- **Hb S/C** - Hb S/C disease

Others

- **CH** - Congenital Hypothyroidism (T4, TSH assay)
- **CAH** - Congenital Adrenal Hyperplasia (luteinizing hormone)
- **Biotinidase** - Biotinidase deficiency (times square colorimetry)
- **GALT** - Classical Galactosemia (fluorescence/MS assay)
- **HEAR** - Hearing Loss (OAE/BAER)
- **CF** - Cystic Fibrosis (IRT Assay)

* disorders seen in the UK Metabolic Clinic
Slide 16

Relation to Case 1?

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
• **Labs:** OT/FSBS – 39, BMP: Glu QNS, BUN/Cr – 45, HCO3<5, AG – 25.
• **Management:** rapid intervention with IVF with 10% dextrose, close IP monitoring, confirmatory testing – MCADD.
• **Outcome:** Now healthy 4 year old on metabolic management.

Slide 17

What are the implications to PCP?

• More and more abnormal screen reports will be made available to PCP
• More and more need to have www.ACMG.net in your office computer browser as favorite.
• More need to familiarize with ACT Sheets and Emergency Protocol
• More acute visits warranting either outpatient or inpatient basic evaluation and management +/- counseling

Slide 18

Case 1 events during childhood

• Presented to ED with episodes of vomiting and low grade temperature ➔ lengthy triage process ➔
  1. Hypoglycemia and acidosis
• Due to Tympanostomy tube placement; fasting 4-5 hours prior to surgery and then kept on NS drip ➔
  1. Hypoglycemia and acidosis
What are the implications?

• More of these children will present to ED and will need prompt and timely care; even if presenting symptoms or complaints of common childhood illnesses

• More of these children will admitted for observation during common illnesses to avert metabolic crisis

• Surgical procedure/ Anesthesia requiring fasting need to be considered carefully

Approach to Metabolic Disorders ......
........which path to take??????
Slide 22

It's only that simple ............

Slide 23

Slide 24

What lab tests and when?

Common (2-4 hrs):
- CBC (anaemia, leukopenia)
- CMP (hyperkalemia, hypokalemia, acidosis, metabolic acidosis, LFT)
- UA – uric acid, ketones, reducing substances, pH, blood urea, proteins
- Ammonia Δ (newborn, <1 mo)
- Lactate (Δ)
- Pyruvate
- Lactate/Pyruvate ratio (Δ, > 10) – plasma and CSF

Specialized Biochemical (1-2 weeks):
- Plasma and Urine Organic Acid Panel
- Plasma Amino Acid Panel
- Plasma Organic Acid Panel and Pyruvate
- Plasma, CSF and Urine Amino Acids

Enzyme Assays and DNA Mutation analysis (> 2-4 weeks)
Slide 25

SUBSTRATE

Endogenous production

Removal

Slide 26

Composition of Diet

Protein

Fat

CHO

Amino acids

Fatty acids

Glucose/others

Organic acids

Organic acids

Cell structure

Energy

Slide 27

Treatment / Management Principles

During acute metabolic crisis –

• Improve hydration

• Eliminate any oral/parenteral source

• Prevent catabolism/stimulate anabolism

• 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
  - D2W or higher + electrolytes @ min. 1.5 M
  - Levocarnitine, Glycine for OA/FAOD **
  - Sodium benzoate, Sodium phenylacetate, Arginine, Citrulline for UCD **
** only in conjunction with a metabolic physician

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 (e.g. Galactosemia, FAOD – VLCADD)
- Utilize alternative pathways (FAOD, OAD, AAD)
- Replacing any deficiencies that develop as a result of the missing or inactive enzyme (Biotinidase deficiency)

Treatment / Management Principles for core metabolic disorders

- 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
Slide 31

Treatment / Management Principles for core metabolic disorders

- **Fatty Acid Oxidation Disorder** – Avoid fasting and dietary fat restriction with essential fatty acid supplementation
- **Galactosemia** – Dietary restriction of lactose
- **Biotinidase Deficiency** – Vitamin supplementation

Slide 32

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

Slide 33

Early acute non specific symptoms in antenatal and neonatal period and…

- Microcephaly – maternal PKU
- Predominant seizures – NKEH, 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, FHH
Slide 34

**Chronic and Progressive generalized symptoms**

- **G I**: anorexia/feeding difficulties, FTT, chronic vomiting, chronic diarrhea
- **Muscle**: hypotonia, poor muscle mass, myopathy, idiopathic non obstructive cardiomyopathy
- **Neurodev**: early nonspecific progressive developmental delay, seizures, hypotonia, ataxia, autistic features, macrocephaly, irritability, myoclonus, polyneuropathy, behavioral d/o

---

Slide 35

**Future.....**

- Newer disorders being considered (LSD, SCID, α1 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)

---

Slide 36

**Future.....**

- 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