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Expanded Newborn Screening in Florida

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Introduction

Newborn Screening in the United States is a public health program with the goal of identifying treatable disorders at birth in order to prevent morbidity and mortality. Technological advances, such as tandem mass spectrometry (MS/MS), allows for the presymptomatic identification of several metabolic disorders before irreversible damage can occur. As a result, the American College of Medical Genetics (ACMG) has recommended that all states expand their programs to screen for a panel of 29 disorders. The State of Florida instituted its expanded newborn screening program in January 2006. While this expansion will improve the outcomes for children with rare metabolic disorders, it introduces the challenges of meeting the educational needs of the medical community, arranging and providing follow up care and addressing the many questions that arise with any change of this magnitude.

History of Newborn Screening

Newborn screening began in the early 1960's with Dr. Robert Guthrie's development of a screening test for phenylketonuria (PKU) which used a small amount of blood placed on filter paper. With the ease of rapid testing, the catastrophic effects of preventable mental retardation were decreased or eliminated. In 1963, Massachusetts became the first state to pass a law requiring PKU screening for all newborn infants. In the following years, screening tests were developed for a number of disorders (such as maple syrup urine disease and galactosemia) where early treatment is essential. State legislatures followed by passing statutes mandating newborn screening. Screened disorders vary from state to state but there is a consensus on the criteria needed for inclusion into a screening panel – 1) the disorder can be identified at a time soon after birth (24-48 hours) where it would not normally be detected, 2) there is a timely and effective test that is both sensitive and specific 3) there are demonstrated benefits to early detection, timely intervention and efficacious treatment.

With the technological advance of tandem mass spectrometry (MS/MS), there is a dramatic increase in the number of disorders that we are able to screen for. In 2005, ACMG released a report recommending an expansion of newborn screening to a uniform panel of 29 disorders. To date, screening of the total uniform panel is required by law and fully implemented in ten states. All but seven states offer expanded newborn screening of metabolic disorders as identified by ACMG.

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Florida's Newborn Screening Program

In January 2006, Florida implemented its expanded Newborn Screening Program. Previously screening for five disorders, the state now screens for 34 disorders. Core conditions, as recommended by the ACMG, Include: hearing loss, endocrine disorders, hemoglobin disorders, a wide spectrum of inborn errors of metabolism plus other genetic disorders (table 1).

Metabolic disorders make up the majority of the expanded newborn screen. With these disorders, the impaired activity of enzymes, transporters, or cofactors results in a lack of necessary metabolic products and/or the accumulation of abnormal metabolites proximal to the metabolic block, which are then processed via alternative pathways. The measurement of these metabolites or their products after conjugation with carnitine is the basis of expanded newborn screening by tandem mass spectrometry (MS/MS).

Expanded MS/MS currently measures two main classes of metabolites: amino acids and acylcarnitine conjugates. With amino acid disorders, levels of one or more amino acids are increased. Other disorders in the intermediary metabolism of amino acids cause organic acidemias, which are detected when an abnormal metabolite is conjugated with carnitine for excretion. In disorders of fatty acid oxidation, fatty acids are conjugated with carnitine and the corresponding acylcarnitines accumulate.

Symptoms of inborn errors of metabolism usually appear early in infancy, although several can become symptomatic in late childhood or adulthood in at least some instances.

Table 1: Florida Newborn Screening Disorders

Abbrev.	Disorder
Endocrine Disorders	
CAH	Congenital adrenal hyperplasia
HYPOTH	Congenital hypothyroidism
Hemoglobin Disorders	
HB S/Th	Hb S/Beta-thalassemia
HB S/C	HB S/C disease
SCA	Sickle cell anemia
Miscellaneous Disorders	
HL	Hearing Loss
BIOT	Biotinidase Deficiency
CF	Cystic Fibrosis (not yet available)
Metabolic Disorders	
	Galactosemias
GALT	Galactosemia (G/G)
	Amino Acid Disorders
ASA	Arginosuccinic acidemia
CIT	Citrullinemia
PKU	Phenylketonuria
HCY	Homocystinuria
MSUD	Maple syrup urine disease
TYR I	Tyrosinemia type I
TYR II	Tyrosinemia type II
	Organic Acid Disorders
BKT	Beto-ketothiolase deficiency (Mitochondrial acetoacetyl-CoA thiolase deficiency
GAI	Glutaric Acidemia I
HMG	3-0H 3-methyl glutaric aciduria
3MCC	3-Methylcrotonyl-CoA carboxylase deficiency
IVA	Isovaleric academia
MCD	Multiple carboxylase deficiency
PA (PROP)	Propionic academia
MMA	Methylmalonic academia Cbl A,B)
MUT	Methylmalonic acidemia (mutase deficiency)
	Fatty Acid Oxidation Disorders
CAT	Carnitine/Acylcarnitine translocase deficiency
CUD	Carnitine uptake defect
CPT-1	Carnitine palmityl transferase deficiency type I
CPT-2	Carnitine palmityl transferase deficiency type II
GA II	Glutaric acidemia type II (Multiple acyl-CoA dehydrogenase deficiency)
LCHAD	Long-chain L-3-OH acyl-CoA dehydrogenase deficiency
MCAD	Medium chain acyl-CoA dehydrogenase deficiency
VLCAD	Very long-chain acyl-CoA dehydrogenase deficiency
SCAD	Short chain acyl-CoA dehydrogenase deficiency
TFP	Trifunctional protein deficiency

Ref: Florida Department of Health www.doh.state.fl.us

With the application of MS/MS for newborn screening, the capability of identifying several analytes and the increased sensitivity have led to the detection of a higher number of patients. It must be emphasized that the initial test is a “screening test”; there is always a risk for false-positive and false-negative results. Special attention must be paid to how questions and referrals are addressed with the parents of any child who screens positive, including reassurance that a positive screen is not a positive diagnosis until it is confirmed. While most infants will turn out not to have the disorder, the confirmatory process is absolutely necessary.

Amino Acid Disorders

Plasma amino acids are used as confirmatory testing for amino acid disorders. Patients with enzyme defects in the catabolism of an amino acid will exhibit very high blood levels of that amino acid. In addition, other amino acids distal to the enzymatic block may be depleted and become conditionally essential. MS/MS allows for the early diagnosis and treatment of patients with amino acid disorders in addition to phenylketonuria, preventing or limiting severe consequences of the disease. Treatment of amino acid disorders requires frequent laboratory monitoring and nutrition management with specialized medical formulas and protein-restricted diets while insuring adequate protein and nutrients for growth and development without elevations in toxic metabolites.

Organic Acidemia

Organic acidemias, involving a large spectrum of disorders and many metabolic pathways, often occur with the catabolic pathways of branched-chain amino acids. However, in most cases, the specific abnormality is not detectable by amino acid analysis. Specific acylcarnitine species accumulate with a metabolic block at any site in the pathway. Primary confirmatory testing includes urine organic acids and a urine acylglycine profile. Plasma acylcarnitine profile is also widely used, but should be ordered in conjunction with urine studies. Urine acylcarnitine profile may give complementary information for identifying borderline patients.

With organic acidemias, a build up of toxic metabolites is triggered by stress such as fasting or viral illness. Metabolic crisis can present with metabolic acidosis, hypoglycemia, ketonuria and hyperammonia requiring efficacious intervention to prevent death. Management includes supplements/medications to drive the lacking pathways as well as specialized protein restricted diets and medical formulas.

Fatty Acid Oxidation Disorders

Many disorders of fatty acid oxidation are episodic, both clinically and biochemically. Therefore, a normal result obtained from an asymptomatic patient does not exclude the disorder. Newborn screening by MS/MS aids in identifying patients before symptoms occur and the newborn screening blood spot is often the most informative sample for detecting a fatty acid oxidation disorder.

Confirmatory testing for fatty acid oxidation disorders may include urine studies for acylcarnitines, organic acids, carnitine and/or acylglycine as well as plasma studies for carnitine and acylcarnitine. In urine organic acids, excess excretion of dicarboxylic acids, especially unsaturated, is a nonspecific sign of defective β-

oxidation. Other abnormal organic acids and acylcarnitine species allow for identification of the specific defect in the β-oxidation cascade.

Fatty acid oxidation is involved in the production of energy in conditions of stress and increased demand. Depletion of glycogen stores and falling glucose levels activate lipid mobilization from fat stores for utilization by the liver, heart and muscle. Fatty acid β-oxidation occurs in mitochondria with at least 20 steps in pathways catalyzed by enzymes with overlapping chain length specificity. While short and medium chain fatty acids are believed to freely cross the mitochondrial membrane, long chain fatty acids (C16 and C18) enter the mitochondrial matrix after conjugation with carnitine. Measurement of acylcarnitine conjugates allows for newborn screening of several of these disorders.

Abnormalities in β-oxidation can result in hypoketotic hypoglycemia, myopathy, cardiomyopathy and sudden infant death syndrome (SIDS).

Inborn Errors of Metabolism in Florida 2006

Since its implementation in January 2006, Florida's expanded newborn screening program has identified thirty-four infants with an inborn error of metabolism (table 2).

Table 2. Inborn Errors of Metabolism identified in 2006.

Category	Metabolic Disorder	#
Amino Acid Disorders	Maple Syrup Urine Ds. (MSUD)	2
	Phenylketonuria (PKU)	9
	Homocystinuria (HCY)	1
Organic Acid Disorders	3-Methylcrotonyl-CoA Carboxylase deficiency (3-MCC)	3
	Isovaleric Acidemia (IVA)	1
Fatty Acid Oxidation Disorders	Trifunctional protein deficiency (TFP)	1
	Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	10
	Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	1
	Glutaric Acidemia, Type 2 (GA2)	1
Other Enzyme Disorders	Biotinidase (BIO)	3
	Galactose Transferase Deficiency-classical (GALT)	2

Ref: Lois Taylor, Director, Florida Newborn Screening Program and National Newborn Screening Information System (NNSIS) database.

Conclusion

With tandem mass spectrometry and other technological advances, the expansion of newborn screening in Florida gives the opportunity to improve the outcomes of patients with rare metabolic disorders. A vast spectrum of disorders can now be identified, some with catastrophic health effects but others with questionable and variable presentations and outcomes. As with any change of this magnitude, other challenges will follow such as insuring accurate diagnosis, treatment and follow up of disorders, providing continued education to the medical community and addressing additional questions that arise with the new information made available.

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Resources

ACMG Newborn Screening Act Sheets, htttp://www.acmg.net /resources/policies/ACT/condition-analyte-links.htm

Florida Department of Health, http://www.doh.state.fl.us

National Newborn Screening and Genetics Resource Center of the US. http:// genes-r-us.uthscsu.edu

National Newborn Screening Information System (NNSIS) database. http://www2.uthscsa.edu/nnsis/

About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20 of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.

Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

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