

In this issue, we are continuing the series of articles put together by Dr. Manoj Ghoda, gastroenterologist in Ahmedabad with an interest in IEMs. This is the third article in the series.

On July 18, 2010, on behalf of IAP, Ahmedabad and 3G (Gujarat Gastroenterology Group), Dr. Ghoda is organizing a day long symposium titled, **“Grand Rounds in Neonatal and Pediatric Liver, GI and Metabolic diseases”**. Please send an email to [mkgghoda@yahoo.com](mailto:mkgghoda@yahoo.com) for additional information.

In the last week of April 2010, Dr. Cariappa and I attended the MENA conference on Newborn Screening in Doha, Qatar. The conference reviewed the status of screening in about 18 countries in the region from Morocco to Pakistan. The region is beginning to take screening seriously with Saudi Arabia the farthest along.

### **IMPORTANT: Availability of Diets**

We have a supply of diets to treat MSUD, MMA/PA, PKU and UCD. If a patient requires the diet, please contact us and we will ship it to you at no charge. Some of these diets expire in August 2010 and we would rather that a patient benefits than it be discarded without benefitting anybody.

The quantity of diets is limited and is a stop gap measure until supplies are received by the patient (We can help you place orders with Nutricia in the UAE). Our only request is that the diets we supplied be replaced so that another patient can be helped, in the future.

### **Clinical Presentations of Inborn Error of Metabolism (IEM)**

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### **First Line Investigations in Metabolic Encephalopathy (Contd. from previous issue)**

#### **Hypoglycemia:**

Hypoglycemia and its associated symptoms occasionally may be seen in infants with disorders of protein intolerance, but it is seen more commonly in disorders of carbohydrate metabolism or fatty acid oxidation (FAOD).

Among the best known inborn errors of metabolism associated with hypoglycemia are the hepatic glycogen storage diseases (GSD). The hypoglycemia

in these disorders is related to the inability of the liver to release glucose from glycogen, and it is most profound during periods of fasting. Hypoglycemia, hepatomegaly, and lactic acidosis are prominent features of these disorders.

Hypoglycemia is not a feature of GSD type II (Pompe disease) because cytoplasmic glycogen metabolism and release are normal in this disorder in which glycogen accumulates within lysosomes as a result of deficiency of the enzyme acid maltase. Clinical manifestations of this disorder include macroglossia, hypotonia, cardiomegaly with congestive heart failure, and hepatomegaly. Cardiomegaly is the most striking feature and may be apparent in the neonatal period. Congestive heart failure is the cause of death in most cases.

Hypoglycemia may be a prominent feature of both galactosemia and hereditary fructose intolerance, although symptoms of the latter disorder occur only after fructose (sucrose) has been introduced in the diet.

A number of inherited defects in FAOD have been identified in infants presenting with hypoglycemia. These disorders are important because of their apparent frequency and because of the variability of the initial presentation. Infants affected have an impaired capacity to use stored fat for fuel during periods of fasting and readily deplete their glycogen stores. Despite the development of hypoglycemia, acetyl CoA production is diminished, and ketone production is impaired. The hypoglycemia occurring in these conditions is typically characterized as nonketotic, although small amounts of ketones may be produced. Hypoglycemia may occur as an isolated finding or may be accompanied by many of the other biochemical derangements typically associated with Reye syndrome, such as hyperammonemia, metabolic acidosis, and elevated transaminases.

Hepatomegaly may or may not be present. Any infant presenting with findings suggesting Reye syndrome should be evaluated for fatty acid oxidation defects. Because the incidence of true Reye syndrome has decreased, most children presenting at any age with this constellation of findings have an inherited metabolic disorder.

The most common of FAODs is medium-chain acyl CoA dehydrogenase deficiency. In addition to presenting as nonketotic hypoglycemia or a Reye's-like syndrome, it may present as sudden death or an



acute life-threatening event. Many reports of infants diagnosed as having medium-chain acyl CoA dehydrogenase deficiency have described a history of a sibling who died of SIDS. Fat accumulation in the liver or muscle of any infant dying unexpectedly should suggest strongly the possibility of this or a related disorder of fatty acid oxidation. Very long-chain fatty acyl CoA dehydrogenase deficiency is associated with similar clinical findings, although there also may be evidence of a cardiomyopathy. Infants with this and several other fatty acid oxidation defects may present with cardiac arrhythmias or unexplained cardiac arrest.

The accumulation of fatty acyl CoAs in patients with fatty acid oxidation defects leads to a secondary carnitine deficiency, probably as a result of excretion of excess acylcarnitines in the urine. Urine organic acid analysis, measurement of serum carnitine, and analysis of the plasma acylcarnitine profile are the most helpful laboratory studies in the initial screening for defects in fatty acid oxidation. These studies are sufficient to establish the diagnosis of medium-chain acyl CoA dehydrogenase deficiency, which is associated with the presence of a characteristic metabolite, octanoylcarnitine, on the acylcarnitine profile. Enzymatic assays may be necessary for the definitive diagnosis of some of the fatty acid oxidation defects. As is true for the defects in carbohydrate metabolism leading to hypoglycemia, treatment of the fatty acid oxidation defects involves avoidance of fasting and provision of adequate glucose. Restriction of dietary fat intake and supplemental L-carnitine therapy are recommended.

### **Abnormal Odor**

Abnormal body or urinary odor, more commonly observed by nurses or mothers rather than by physicians, is an important but often overlooked clue to the diagnosis of several of the inborn errors of metabolism and may be the most specific clinical finding in these patients. In the acutely ill infant with an abnormal odor, isovaleric acidemia (IVA), glutaric acidemia type II (GA2), and maple syrup urine disease (MSUD) are the most likely entities to be encountered. In MSUD, the urine has a distinctive sweet odor, said to be reminiscent of maple syrup or burnt sugar. The odor associated with IVA and GA-2 is pungent and unpleasant and similar to that of sweaty feet.

### **Samples to Obtain From a Dying Child with a Suspected Inborn Error of Metabolism:**

If death appears imminent in a child suspected of having an inborn error of metabolism, it is important to obtain the appropriate samples for postmortem analysis. This is critical for resolution of the cause of death and is essential for subsequent genetic counseling and prenatal diagnosis. The following samples should be collected and stored: urine, frozen; plasma, separated from whole blood and frozen; and a small snip of skin obtained using sterile technique and stored at room temperature or 37°C in tissue culture medium, if available, or sterile saline.

If an autopsy is performed, a sample of unfixed liver tissue should be obtained as soon as possible after death and frozen at -20°C for subsequent biochemical studies. Additional tissue should be preserved for electron microscopy. If consent for autopsy is denied, consent for a postmortem needle biopsy of the liver can be requested. The liver tissue should be frozen in total or in part if histologic studies appear to be indicated. As soon as possible after death, the case should be reviewed with a metabolic specialist and plans made for the transport of samples to the appropriate laboratory.

Recent advances in diagnosis and treatment have improved significantly the prognosis for many infants with inborn errors of metabolism. Early clinical diagnosis is essential in ensuring that affected infants will receive the benefits of these advances. It is hoped that the guidelines presented in this review will assist the physician in the recognition of infants who may have an inborn error of metabolism and in the initial evaluation and stabilization of these patients.

### **Logistics, Kits, Reports**

Please send e-mail to [info@neogenlabs.com](mailto:info@neogenlabs.com) in case you need kits, looking for reports or any general question. You can expect a reply or call within 24 hours (except for holidays) to address your request.

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[www.neogenlabs.com](http://www.neogenlabs.com)

## First Step Newborn Screening Panel

### ACYLCARNITINE PROFILE (MS)

#### Fatty Acid Oxidation Disorders

- Carnitine / Acylcarnitine Translocase Deficiency
- Carnitine Palmitoyl Transferase Deficiency Type I
- 3-Hydroxy Long Chain Acyl-CoA Dehydrogenase Deficiency
- 2,4-Dienoyl-CoA Reductase Deficiency<sup>1</sup>
- Medium Chain Acyl-CoA Dehydrogenase Deficiency
- Multiple Acyl-CoA Dehydrogenase Deficiency
- Neonatal Carnitine Palmitoyl Transferase Deficiency Type II
- Short-chain Acyl-CoA Dehydrogenase Deficiency
- Short chain Hydroxy Acyl-CoA Dehydrogenase Deficiency
- Trifunctional Protein Deficiency
- Very Long Chain Acyl-CoA Dehydrogenase Deficiency

#### Organic Acid Disorders

- 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency
- Glutaric Acidemia Type I
- Isobutyryl-CoA Dehydrogenase Deficiency
- Isovaleric Acidemia
- 2-Methylbutyryl-CoA Dehydrogenase Deficiency
- 3-Methylcrotonyl-CoA Carboxylase Deficiency
- 3-Methylglutaconyl-CoA Hydratase Deficiency
- Methylmalonic Acidemias
  - Methylmalonyl-CoA Mutase Deficiency
  - Some Adenosylcobalamin Synthesis Defects
  - Maternal Vitamin B12 Deficiency
- Mitochondrial Acetoacetyl-CoA Thiolase Deficiency
- Propionic Acidemia
- Multiple CoA Carboxylase Deficiency
- Malonic Aciduria

### AMINO ACID PROFILE (MS)

#### Amino Acid Disorders

- Argininemia
- Argininosuccinic Aciduria
- 5-Oxoprolinuria
- Carbamoylphosphate Synthetase Deficiency
- Citrullinemia
- Homocystinuria
- Hypermethioninemia
- Hyperammonemia, Hyperornithinemia, Homocitrullinuria Syndrome
- Hyperornithinemia with Gyral Atrophy
- Maple syrup disease
- Phenylketonuria
  - Classical/Hyperphenylalaninemia
  - Biotin Cofactor Deficiencies
- Tyrosinemia
  - Transient Neonatal Tyrosinemia
  - Tyrosinemia Type I
  - Tyrosinemia Type II
  - Tyrosinemia Type III

### OTHER (MS)

- Hyperalimantation
- Liver Disease
- Medium Chain Triglyceride Oil Administration
- Presence of EDTA Anticoagulants in blood specimen
- Treatment with Benzoate, Pyvalic Acid, or Valproic Acid
- Carnitine Uptake Deficiency

### BIOCHEMICAL ANALYSIS (BIO)

- Galactosemia (GALT)
- Congenital Hypothyroidism (CH)
- Congenital Adrenal Hyperplasia (CAH)
- G6PD
- Cystic Fibrosis
- Biotinidase (BIOT)

### Screening Panels

#### MS - Mass Spectrometry Panel (45+ Disorders)

(45 IEMs, includes Fatty Acid Oxidation Disorders, Amino Acid Disorders, and Organic Acid Disorder panels)

#### BIO - Biochemical Panel (6 Disorders)

CH, CAH, G6PD, GALT, CF, BIOT

- **First Step PLUS** MS/Bio6 Rs. 4,250/-
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- **First Step MS** MS Rs. 3,250/-
- **First Step Bio6** BIO Rs. 2,000/-
- **First Step Bio4** CH/CAH/GALT/G6PD Rs. 1,500/-