

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

My goal was to keep the newsletter to one page of content so that it will be an easy read. I have deviated from that rule so that I could include the comprehensive articles by Dr. Ghoda, which are very informative and will help physicians in identifying and treating IEMs.

Dr. Cariappa and I will be attending the MENA conference on Newborn Screening in Qatar at the end of April 2010.

We have partnered with **BabyCell**, a company in the cord blood banking business, to offer newborn screening to their customers.

## 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. The quantity of diets are 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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### Acute Metabolic Encephalopathy

Several groups of IEMs, notably the organic Acidemias (OA), urea cycle defects (UCD) and certain amino acid (AA) disorders, typically present with acute life threatening symptoms of an encephalopathy. These symptoms are the result of toxic effects of accumulating metabolites on the central nervous system (CNS). Since most of these metabolites cross the placenta and are cleared by the mother during gestation, affected infants usually appear normal at birth. The interval between birth and the onset of clinical symptoms ranges from hours to months. The initial findings are usually those of lethargy and poor feeding, as seen in almost any sick infant. Although sepsis is often first considered in infants who present in this way, these symptoms in a full-term infant with no specific risk factors strongly suggest an IEM. It is author's suggestion that IEM

must be very near the top of differential diagnosis of neonatal sepsis.

Infants with IEMs may become debilitated and septic rather quickly, and it is therefore important that the presence of sepsis not exclude consideration of other possibilities. Put it the other way, presence of sepsis must mandate a historical, clinical and biochemical search for underlying IEM. If untreated, the lethargy associated with these conditions may progress to coma. Other signs of CNS dysfunction, such as seizures and abnormal muscle tone, also may be noted. Evidence of cerebral edema may be observed, and intracranial hemorrhage occasionally occurs.

An infant with an IEM who presents more abruptly or in whom the lethargy and poor feeding go unnoticed may first come to attention because of apnea or respiratory distress. The apnea is typically central in origin and a symptom of the metabolic encephalopathy, but tachypnea may be a symptom of an underlying metabolic acidosis, as occurs in OA.

Infants with UCD and evolving hyperammonemic coma initially exhibit central hyperventilation, which leads to respiratory alkalosis. Any neonate with respiratory alkalosis must be considered a candidate for UCD. Ammonia must be obtained in such cases.

**Vomiting** is a striking feature of many of the IEMs associated with protein intolerance, although considerably less common in the newborn than in the older infant. If persistent vomiting occurs in the neonatal period, it usually signals significant underlying disease. IEMs should always be considered in the differential diagnosis.

### First Line Investigations in Metabolic Encephalopathy Ammonia

Among the most important laboratory findings associated with IEMs presenting with an acute encephalopathy is hyperammonemia. Significant hyperammonemia is observed in a limited number of conditions. UCDs, OAs and fatty acid oxidation disorders (FAOD) are at the top of the list. Ammonia levels in newborns with these conditions frequently exceed 1000  $\mu\text{mol/L}$ . Marked hyperammonemia provides an important clue to diagnosis and indicates the need for urgent treatment to reduce the ammonia level.



## Hyper ammonemia

- \* **Urea cycle disorders (UCD)**
- \* **Organic Acidemia (OA)**
- \* **Fatty Acid Oxidation Disorders (FAOD)**
- \* **Acute Liver Failure**

The degree of neurologic impairment and developmental delay observed subsequently in affected infants has been shown to be dependent on the duration of the neonatal hyperammonemic coma. Transient hyperammonemia of the Newborn (THAN) is a condition seen in a newborn for no obvious reason and subsides on its own.

High ammonia is also seen in liver disorders but here you should see abnormal liver functions like conjugated bilirubin, transaminases and prothrombin time. Again, in liver diseases the level of ammonia is not in thousands but hundreds and generally 2 to 5 times that of normal.

The timing of the onset of symptoms may provide an important clue. Patients with some of the OAs, such as Glutaric Acidemia Type II or with Pyruvate Carboxylase (PC) deficiency, may exhibit symptomatic hyperammonemia during the first 24 hours. Symptoms in the first 24 hours also are characteristic of THAN, a condition that is poorly understood but apparently not genetically determined. The typical patient with this disorder is a large, premature infant (mean gestational age of 36 weeks) who has symptomatic pulmonary disease, often from birth, and severe hyperammonemia. The condition can occur in full-term infants, however, including those without respiratory symptoms. Survivors do not have recurrent episodes of hyperammonemia and may or may not exhibit neurologic sequelae.

Infants who develop severe hyperammonemia after 24 hours of age usually have a UCD or an OA; Infants with OAs typically exhibit metabolic acidosis as well. Urine organic acid analysis should always be obtained, regardless of whether acidosis is present or not. Metabolic acidosis is not a typical feature of UCDs. Plasma amino acid analysis is helpful in the differentiation of the specific defects in this group.

In addition, Carbamyl Phosphate Synthetase deficiency and Ornithine Transcarbamylase (OTC) deficiency may be differentiated by measuring urine orotic acid, which is low in the former and elevated in the latter. Unfortunately, this test is not routinely available in India. Although the family history is often negative, a positive history of early male deaths or females with episodic illness in the family of a male infant with hyperammonemia suggests Ornithine Transcarbamylase Deficiency, the only one of the UCDs with a sex-linked mode of inheritance.

Less significant elevations of plasma ammonia than those associated with IEMs and THAN can be observed in a variety of other conditions associated with liver dysfunction, including sepsis, and perinatal asphyxia. Liver function studies should be obtained in evaluating the significance of moderate elevations of plasma ammonia. However, even in cases of severe hepatic necrosis, it is rare for ammonia levels to exceed 500  $\mu\text{mol/L}$ . Mild transient hyperammonemia with ammonia levels as high as twice normal is relatively common in the newborn, especially in the premature infant, and is usually asymptomatic. It appears to be of no clinical significance, and there are no long-term neurologic sequelae.

### Bedside differentiation of hyperammonemia

Very High: > 10 ULN:	Consider UCD, OA, FAOD.
Mild to Moderate with Respiratory Alkalosis:	Consider UCD.
With Significant Hepatocellular Damage:	Consider liver diseases.

### **Metabolic Acidosis**

The second important laboratory feature of many of the IEMs during acute episodes of illness is metabolic acidosis with an increased anion gap.

Among the IEMs, the largest group is associated with overwhelming metabolic acidosis in infancy is the group of OAs, including Methylmalonic Acidemia, Propionic Acidemia, and Isovaleric Acidemia.



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In addition to specific OA intermediates, plasma lactate often is elevated in OAs as a result of secondary interference with co-enzyme A (CoA) metabolism. Neutropenia and thrombocytopenia are commonly observed and further confuse these disorders with neonatal sepsis. Hyperammonemia, sometimes as dramatic as that associated with UCDs, is commonly but not uniformly seen in clinically ill infants with OAs.

Defects in pyruvate metabolism or in the respiratory chain may lead to primary lactic acidosis presenting as severe metabolic acidosis in infancy. Unlike most of the other conditions presenting acutely in the newborn, clinical features of these disorders are unrelated to protein intake. Disorders in this group should be considered in patients with lactic acidosis who have normal urine organic acids.

Differentiation of the various disorders in this group can be facilitated by measuring plasma pyruvate and calculating the lactate/pyruvate ratio. A normal ratio ( $\leq 25$ ) suggests a defect in pyruvate dehydrogenase (PDH) or in gluconeogenesis, and an elevated ratio ( $\geq 25$ ) suggests PC deficiency, a respiratory chain defect, or a mitochondrial myopathy.

Other tests may also be required if the suspicion of an IEM is strong. Amongst them most common are AA and OA, analysis of which can be obtained in any part of the country through reference laboratories.

### **Emergency Treatment of the Infant with an Acute Metabolic Encephalopathy**

When an IEM is suspected, immediate treatment should be initiated, even if a definitive diagnosis may not yet be established. Appropriate and aggressive treatment before the confirmation of a diagnosis may be life saving and may avert or reduce the neurologic sequelae of some of these disorders.

The immediate treatment of infants with disorders in this group has two primary goals; the first is the removal of accumulating metabolites such as organic acid intermediates or ammonia. At the first suspicion of a disorder associated with protein intolerance, protein intake should be discontinued immediately.

In critically ill infants with hyperammonemia, arrangements should be made for urgent hemodialysis. Peritoneal dialysis, continuous

arteriovenous hemoperfusion, and exchange transfusion all are inferior to hemodialysis. Unfortunately most of the renal units are not geared to hemodialysis in newborns.

In patients suspected of having UCD because of significant hyperammonemia without acidosis, an infusion of 6 mL/kg of 10% arginine HCL (0.6 g/kg) can be given intravenously over 90 minutes. In patients with Citrullinemia and Argininosuccinic Aciduria, this often results in a precipitous drop in the plasma ammonia level.

If an OA is suspected, vitamin B12 (1 mg) should be given intramuscularly in case the patient turns out to have a B12 responsive form of Methylmalonic Acidemia. Biotin (10 mg) should be given orally or by Ryle's tube, because some patients with multiple carboxylase deficiency are biotin responsive.

If acidosis exists, intravenous bicarbonate should be administered liberally. Calculations of bicarbonate requirements appropriate for the treatment of other conditions are rarely adequate in these disorders because of ongoing production of organic acids or lactate. The acid-base status should be monitored frequently, with therapy adjusted accordingly.

Dialysis should be considered for severely acidotic neonates with OAs, regardless of whether hyperammonemia is present. After removing toxic metabolites, the second major goal of therapy in infants with IEMs should be to prevent catabolism. Intravenous glucose should be administered liberally to provide as many calories as possible. Intravenous lipids can be given to infants with UCDs and other disorders in which dietary fat plays no role. Protein should not be withheld indefinitely. If clinical improvement is observed and a final diagnosis has not been established, some amino acid intake should be provided after a maximum of 2 to 3 days of complete protein restriction. Essential amino acids or total protein can be provided orally or intravenously at an initial dose of 0.5 g protein/kg/24 hours. This should be increased incrementally to 1.0 g/kg/24 hours and held at that level until the diagnostic evaluation is complete and plans can be made for definitive long-term therapy.



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## March 2010 Statistics

- 1 Case of Biotinidase (BIOT)
- 2 Cases of CAH
- 1 Case of CH
- 1 Case of CPT II
- 6 Cases of G6PD Deficiency
- 1 Case of HCY, TYR, Liver Disease
- 2 Cases of MADD
- 1 Case of 3MCC, HMG Lyase, 3MGA Hydratase
- 1 Case of MMA/PA
- 2 Cases of SCAD
- 1 Case of VLCADD

## Case Presentation

If you have an interesting case that you would like to include in NBS News, please let us know.

## 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.

## IMPORTANT:

Please ensure that the cheque or DD is made out to, **NeoGen Labs Private Limited** payable at Bangalore.

**Thomas Mookken, CEO**

T: +91 99006 55115

[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)

- Hyperalimentation
- 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/-)
- **First Step** MS/Bio4 (Rs. 3,975/-)
- **First Step MS** MS (Rs. 3,250/-)
- **First Step Bio6** BIO (Rs. 2,000/-)
- **First Step Bio4** CH/CAH/GALT/G6PD (Rs. 1,500/-)