Review Article

Recognition and diagnostic approach to acute metabolic disorders in the neonatal period

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ABSTRACT

Inborn errors of metabolism (IEM) constitute a group of inherited disorders that cause significant neonatal morbidity and mortality. This diverse group of diseases present with different clinical manifestations that make the diagnosis a real challenge. Early detection and appropriate investigations prevent complications and save lives. The aim of this review is to enable general paediatricians to clinically recognize IEM and plan relevant investigations at the appropriate time in a cost-effective manner, especially in countries where resources are limited.

Key words: Inborn errors; Metabolism; Neonate; Diagnosis

The concept of inborn errors of metabolism (IEM) was introduced by Archibald Garrod in 1909[1]. One of the major milestones in the development of this branch of medicine was the description of phenylketonuria (PKU) by Folling in 1934 [1, 2]. The incidence of IEM ranges from 1 in 500 to 1 in 1500 births [1, 3, 4- 6]. Genetic diversity among Arabs, high rates of inbreeding and large family size are optimal for the manifestation of many autosomal recessive disorders including IEM [7]. Newborn screening in Qatar and Saudi Arabia has confirmed that some IEM are more prevalent in the Arab World especially homocystinuria, organic aciduria, and maple syrup urine disease [4-6]. In view of high incidence of consanguinity in Sudan, IEM are widely spread among ethnic groups [8]. Sudan is one of the first Arab countries to document on existence of IEM, with phenylketonuria reported in 1964 and galactosemia in 1965 by Hassan [9, 10]. Individually these disorders are rare, however collectively they account for a large number of acutely sick neonates. Early diagnosis and management is crucial in order to prevent morbidity and mortality [1, 2, 3, 11]. The aim of this review is to assist general paediatricians to recognize features suggestive of IEM in neonates and to draw a rational plan for investigation of these patients.

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Pathophysiology

IEM are mainly caused by genetic mutations and result in deficiency of an enzyme or a cofactor. This usually leads to accumulation of a substrate that can't be metabolized by the deficient enzyme. The resulting pathophysiological process leads to deficiency of a product that is essential for the physiological function of the cell [1, 2, 3, 11]. This mechanism is nicely illustrated by deficiency of the enzyme phenylalanine hydroxylase (PAH) which normally converts phenylalanine to tyrosine. Deficiency of PAH results in accumulation of phenylalanine which is toxic to the brain and deficiency of tyrosine which is essential for melanin formation [1, 2]. Hence, PKU presents with developmental delay and fair color of the eyes and hair. Deficiency of tetrahydrobiopetrin, a cofactor of PAH, results in clinical features similar to PKU [2, 3, 12]. Rarely IEM may result from lack of accessibility of a substance to the cell rather than deficiency of the enzyme as in cystinosis [1, 2].

Classification

In order to make IEM as easy and clear as possible, metabolic disorders presenting in the neonatal period can be classified into five groups, namely protein, carbohydrate and energy, fat, macromolecules disorders, and other disorders [1, 2, 11].

1-Disorders of protein

This constitutes aminoacidopathy like tyrosinemia, maple syrup urine disease and homocystinuria, organic aciduria such as methylmalonic aciduria (MMA), and urea cycle defects such as ornithine transcarbamylase (OTC) deficiency.

2-Carbohydrate and energy disorders

Theses include, but not limited to, galactosemia, glycogen storage diseases, and mitochondrial disorders.

3-Fatty acid disorders

This group includes fatty acid oxidation defects, carnitine disorders, ketogenesis defects (patient can't produce ketones), and ketolytic defects (patients cannot utilize ketones).

4-Macromolecules disorders

This group includes lysosomal and peroxisomal disorders.

5-Other disorders

These include vitamin disorders such as biotinidase deficiency and other rare conditions such as purine and pyrmidine disorders

Clinical approach to IEM

In order to reach a precise diagnosis, a thorough history, a comprehensive physical examination and rational plan of investigation should be in place. IEM in the neonatal period present in two ways:

1. Detection through universal newborn screening in asymptomatic babies
2. Presentation clinically with symptoms and signs. These patient are occasionally very sick and may have significant morbidity and mortality if the diagnosis and appropriate management are delayed [2, 11, 13-16].

Universal newborn screening

Newborn screening is a search for diseases in a large unselected population before the disease is clinically apparent. The objective of newborn screening is to identify affected infants before they become symptomatic. To qualify for screening the disease has to be relatively prevalent, treatable and if not treated has high morbidity and mortality [1, 2, 17, 18]. The test used for screening should be inexpensive (cost effective), sensitive, specific and acceptable to the clients. Diseases detectable by newborn screening include aminoacidopathies such as PKU, fatty acid oxidation defects, organic acidurias, endocrinopathies,

haemglobinopathies, and others such as biotinidase deficiency [19, 20)]. Newborn screening is generally performed by taking blood in a filter paper by heel prick. It is usually done between day two and four of life. Once a positive screening result is received, a confirmatory test together with review of the patient, and possible starting treatment may occasionally be needed on urgent basis depending on the result and the disorder detected. False positive and, to a lesser extent, false negative results may occur. Support for families awaiting confirmation of IEM in their babies is extremely important during this stressful time for the families.

Clinical presentation of IEM in neonates

Metabolic disorders in the neonatal period may present suddenly, gradually or insidiously. Physicians need to have high index of suspicion to think of and diagnose these disorders. Metabolic disorders should be considered in any sick neonate. This includes sick neonates with unexplained sepsis-like features. IEM in neonates present mainly in one of three ways:

1. Energy insufficiency: mainly hypoglycemia and lactic acidosis associated with disorders such as hyperinsulinism, glycogen storage diseases and mitochondrial disorders.
2. Intoxication: due to accumulation of toxic substances such as galactose in galactosemia, leucine in MSUD, and ammonia in urea cycle defects.
3. Dysmorphic features which are mainly associated with storage diseases [1-3, 11, 13-15].

In this review we discuss the first two presentations as the third way of presentation is usually not acute and in most cases not amenable to treatment.

History

Important points in the history include:

-History of consanguinity, as the vast majority of IEM are autosomal recessive conditions.

-History of maternal HELP (hemolysis, elevated liver enzymes and low platelets) may be associated with fatty acid oxidation defect in the new born baby, namely LCHAD (Long chain acylcoenzyme A dehydrogenase) [1, 2, 11, 14].

-Family history of a sibling with metabolic disease or unexplained developmental delay should increase the suspicion of IEM.

-Family history of unexplained neonatal death or sudden infant death syndrome (SIDS) should raise the flag for the possibility of IEM.

-IEM may present with symptoms free period after birth (intoxication group) as the toxic metabolites are not yet accumulated in the first or second day of life. This is a characteristic of protein disorders such as MSUD, organic aciduria and tyrosinemia. Galactosemia may also present after few days symptoms free period [1, 2, 11, 13, 14].

-The age of presentation may give a clue to the diagnosis. For example, newborn babies presenting with symptoms of severe persistent hypoglycemia are likely to have hyperinsulinism. [2, 4, 13]

-The initial presenting symptoms of most IEM are nonspecific such as poor feeding, vomiting and lethargy. This is typical of the intoxication group such as MSUD. As sepsis presents in a similar way, it is sometimes difficult to differentiate sepsis from IEM. The two conditions occasionally co exist. It is reasonable to consider IEM in the differential diagnosis of unexplained illness especially severe sepsis in neonates.

-The progression of the symptoms may give a hint towards the diagnosis of IEM. This is a characteristic of the intoxication group where babies present with symptoms free period followed by nonspecific symptoms such as poor feeding and vomiting that progress to symptoms of encephalopathy such as lethargy, seizures, and coma.

-IEM may affect most of the body systems and accordingly present with systemic symptoms such

as difficulty in breathing, prolonged jaundice, and bleeding disorder.

Physical Examination

Comprehensive and focused physical examination is the key to reach a diagnosis in a timely manner. General condition of the baby may raise the suspicion of IEM. Sick looking baby may suggest intoxication especially in presence of stigmata of encephalopathy such as lethargy, seizure, hypotonia, and coma [2, 4, 13].

Important clues which may indicate IEM include:

-Presence of dysmorphic features suggest macromolecule disorders (peroxisomal and lysosomal diseases) and possible mitochondrial disorders. Most of carbohydrate and protein metabolic disorders don't present with dysmorphic features in the neonatal period [2, 16].

-Eye examination is the window for diagnosing some of the IEM. For instance, cataract in a neonate is highly suggestive of galactosemia. Cataract may be found as early as the first day of life in newborn babies with galactosemia [1, 2].

-Abnormal odor of the neonate is a useful sign of metabolic disorders. Examples of characteristic odors associated with IEM include [1, 2]:

MSUD: maple syrup

Tyrosinemia: boiled cabbage

3 Methylcrotonylglycinuria: fish

Glutaric aciduria type 2: sweaty feet

-Tachypnea with respiratory acidosis in a sick neonate may suggest urea cycle defect. As hyperammonemia is a stimulant to the respiratory center.

-Clinical evidence of cardiomyopathy such as cardiomegaly may raise the suspicion of fatty acid oxidation defect, gluteric aciduria type 2, Pompe's disease, mitochondrial disorder and systemic carnitine deficiency [21, 22, 23].

-Jaundice, bleeding tendency and hepatomegaly may suggest metabolic liver disease such as galactosemia, tyrosinemia and mitochondrial disorder.

Approach to the investigation of IEM

At the end of a detailed clinical assessment, including a focused history and clinical examination, the physician should have a reasonable impression as to the possibility of IEM and what type of disorders, according to the simple classification mentioned above [2,11,24, 25]. In order to use the resources in a cost effective manner, the plan of investigation is classified into three steps. The first step is baseline investigations which is applied for all sick neonates (Table 1). Measurement of blood gas and calculation of the anion gap gives invaluable information and direct the investigations according to the differential diagnosis. Metabolic acidosis with normal anion gap [10-15] indicates that the patient looses bicarbonate through either the kidney or the gut. Increased anion gap shows that acid accumulates. Acid could be lactic acid like in mitochondrial disorders, organic acid as in organic aciduria, or ketoacids as in ketolytic defects and organic acidurias [24, 25]. Supportive investigations may be needed according to the clinical scenario. These include chest X-ray, Echocardiography, cranial ultrasound and complete septic screening including cerebrospinal fluid (CSF) examination. When the suspicion of IEM is higher, one would request second line biochemical investigations (Table 2). Acylcarnitines are conjugates of organic acids with carnitine. Acylcarnitines arise from fatty acid and amino acid catabolism. Acylcarnitine and amino acids are measured by tandem mass spectrometry (MS/MS) machine using a filter-paper blood sample. Organic acids are measured by gas chromatography mass spectrometry (GC/MS) machine [24, 25]. Measurement of amino acids, acylcarnitine profile and organic acids provides an insight to the metabolism and disorders of fatty acid oxidation, organic aciduria, and aminoacidopathy. The third line investigations are specific, confirmatory, and occasionally highly specialized that need to be mostly guided by a pediatrician with some experience in dealing with IEM (Table 3).

Table 1 - First line investigations of neonates with possible IEM

Investigation
Full blood count
Liver function test
Renal function test
Blood gas
Anion gap
Glucose
Lactate
Ammonia
Urine for ketones
Urine for reducing substances

IEM – inborn errors of metabolism.

Table 2 - Second line investigations for neonates with IEM

Investigation
Serum amino acids
Total and free carnitine
Acyl carnitine profile
Urine for organic acids
Beutler test (Galactose-1-phosphate uridyltransferase level)

IEM – inborn errors of metabolism.

Table 3 - Third line investigations for neonates with IEM

Investigation	Indication
Serum lactate, pyruvate	Clinical diagnosis of mitochondrial disorder
CSF lactate, pyruvate	Strong clinical suspicion of mitochondrial disorder
CSF neurotransmitter	Strong clinical suspicion of neurotransmitter diseases
CSF/serum glycine ratio	Clinical diagnosis of non-ketotic hyperglycinemia
Transferin isofocusing	Clinical diagnosis of CDG
Very long chain fatty acids	Clinical diagnosis of peroxisomal disorders
Serum biotindase	Suspicion of biotinidase deficiency
Urine oligosaccharides	Clinical diagnosis of lysosomal disorders
Urine mucopolysachridosis	Clinical diagnosis of mucopolysachridosis
Enzyme assay	Biochemical diagnosis confirmed, enzyme known
DNA study	Biochemical diagnosis known, mutation known
Skin/muscle biopsy	Enzyme or gene expressed in skin or muscle

CDG - congenital disorder of glycosylation, CSF - cerebrospinal fluid, IEM - inborn errors of metabolism.

Clinical pearls

To consolidate the above clinical approach and to address the presumed innate difficulties of IEM, some clinical scenarios are discussed. In practice sometimes physician may face a neonate with clinical phenotype that suggests a specific diagnosis. In this case one would request the relevant appropriate laboratory tests. For example, if a neonate presented in the first day of life with intractable seizure, hypotonia, hiccup, and respiratory difficulties, one would think of non-ketotic hyperglycinemia. Accordingly, the diagnostic plan would include electroencephalography (EEG) for burst suppression pattern, serum and CSF glycine which may shows CSF/serum glycine ratio > 0.06. The next step would be DNA study of the glycine cleavage gene that confirms the diagnosis [1, 2, 11, 14, 26].

A neonate who presents with jaundice, elevated liver enzymes, and coagulopathy should raise the suspicion of metabolic liver disease such as glactosemia and tyrosinemia in addition to the commonly occurring neonatal sepsis. The differential diagnosis includes rare disorders such as mitochondrial depletion syndrome, neonatal hemochromatosis, peroxisomal disorders, and bile acids disorders [2, 11, 13, 27]. The initial diagnostic work up includes detailed liver function tests,lactate, urine for reducing substances, serum amino acids, urine organic acids, and blood galactose-1-phosphate uridyltransferase (G1PUT) level. High serum tyrosine together with increased urine succinylacetone confirms the diagnosis of tyrosinemia type 1. Most of patients with galactosemia show positive reducing substances in the urine in addition to low G1PUT. If the diagnosis of tyrosinemia and galactosemia is excluded, the next step would be investigations of rarer metabolic liver diseases. This includes serum very long chain fatty acids (VLCFA) which is elevated in peroxisomal disorders, and serum and urine bile acid profile which shows abnormalities in bile acid disorders. In neonatal hemochromatosis, serum alpha fetoprotein is grossly elevated [1, 2]

Neonates presenting with cardiomyopathy should be investigated thoroughly to exclude treatable metabolic disorders like systemic carnitine deficiency. Work up in this situation includes, acylcarnitine profile, total and free carnitine, skin biopsy for fatty acid oxidation, DNA, and enzyme assay.

Neonates may present with symptom free period followed by non specific symptoms and then symptoms of acute neonatal encephalopathy such as seizure and coma. In addition to sepsis the differential diagnosis in this scenario includes MSUD, urea cycle defects, organic academia, galactosemia, and tyrosinemia. Patients with encephalopathy are investigated according to the plan outlined in Tables 1, 2, 3, and 4 [28-33].

Neonates who have persistent hypoglycemia need critical samples taken at the time of hypoglycemia as outlined in Table 5. Absence of ketones in the urine limits the differential diagnosis to the following conditions: fatty acid oxidation defect, hyperinsulinism, and ketone formation disorders (ketogenesis disorders) [1, 2, 11]. On the other hand, causes of ketotic hypoglycemia include: hormonal deficiency like cortisol, growth hormone and ACTH. Other differential diagnosis includes glycogen storage diseases and disorders of protein metabolism, as outlined in the above mentioned classification (Table 6).

In conclusion, a pediatrician dealing with sick neonates would identify patients with IEM if index of suspicion is increased coupled with a rational use of resources. Critical metabolic thinking is occasionally the vehicle for the accurate diagnosis (Table 7).

Table 4 - Common metabolic causes of neonatal encephalopathy and key tests

Cause	Key tests
Urea cycle defect	Ammonia, serum amino acids, urine orotic acid
Organic aciduria	Acylcarnitine profile, urine organic acids
Maple syrup urine disease	Serum amino acids
Non-ketotic hyperglycinemia	CSF/serum glycine
Galactosemia	Beutler test
Tyrosinemia	Serum amino acid, urine succenylacetone
Mitochondrial disorders	Serum and CSF lactate

CSF - cerebrospinal fluid.

Table 5 - Critical samples for neonates with persistent hypoglycemia

Investigation
Serum glucose
Lactate
Blood gas/anion gap
Insulin
Cortisol
Growth hormone
Free fatty acids
Serum Ketone bodies
Ammonia
Total and free carnitine
Acylcarnitine profile
Urine organic acids
Urine ketone bodies

Table 6 - Approach and causes of persistent neonatal hypoglycemia

Ketotic hypoglycaemia	Non- ketotic hypoglycaemia
Hormone deficiency	Hormone excess
© Cortisol, Growth hormone, ACTH	© Hyperinsulinism
Metabolic causes	Metabolic causes
© Glycogen storage diseases	© Fatty acid oxidation defects
© Organic aciduria	© systemic carnitine deficiency
© Mitochondrial disorders	© Ketogenesis defects
© Ketolytic defects	

ACTH - Adrenocorticotrophic Hormone

Table 7 - When should we think metabolic?

Condition
Acute unexplained illness in a neonate
Neonatal encephalopathy
Unexplained cardiomyopathy
Persistent hypoglycaemia
Elevated liver enzymes with coagulopathy
Metabolic acidosis with increased anion gap
Ketoacidosis

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