

INBORN ERRORS OF METABOLISM (IEM): APPROACH TO DIAGNOSIS AND EARLY MANAGEMENT IN A SICK CHILD

Introduction

Over 300 human diseases due to IEM are now recognized and a significant number of them are amenable to treatment.

IEMs may present as

- an acute metabolic emergency in a sick child
- chronic problems involving either single or multiple organs, either recurrent or progressive, or permanent

It will become ever more important to initiate a simple method of clinical screening by first-line paediatric doctors with the goal 'Do not miss a treatable disorder'.

Classification

From a therapeutic perspective, IEMs can be classified into five useful groups:

Table 1. Classifying IEM disorders from a therapeutic perspective

Group 1. Disorders that give rise to acute intoxication	
<i>aminoacidopathies</i>	Specific emergency and long term treatment available for most diseases
maple syrup urine disease, tyrosinaemia, PKU*, homocystinuria*	
<i>most organic acidurias</i>	
methylmalonic, propionic, isovaleric, etc.	
urea cycle defects	
<i>sugar intolerances</i>	
galactosaemia, hereditary fructose intolerance	
<i>defects in long-chain fatty acid oxidation</i>	
	(* chronic intoxication)
Group 2. Disorders with reduced fasting tolerance due to cytoplasmic energy defects	
<i>disorders of glucose homeostasis</i>	Specific emergency and long term treatment available for most diseases
glycogen storage diseases, disorders of gluconeogenesis	
<i>fatty acid oxidation defects</i>	
<i>disorders of ketogenesis/ketolysis</i>	
Group 3. Disorders of neurotransmission	
<i>non ketotic hyperglycinemia</i>	Some are treatable
<i>disorders of biogenic amine metabolism</i>	
<i>disorders of GABA metabolism</i>	
<i>pyridoxine- /pyridoxal phosphate-/folinic acid-responsive seizures</i>	
<i>glucose transporter (GLUT1) deficiency</i>	
Group 4. Disorders involving complex molecules	
<i>lysosomal storage disorders</i>	Very few are treatable
<i>peroxisomal disorders</i>	
<i>congenital disorders of glycosylation</i>	
<i>creatine biosynthesis disorders</i>	
<i>sterol biosynthesis disorders</i>	
<i>purine metabolism disorders</i>	
Group 5. Disorders of mitochondrial energy defects	
<i>respiratory chain enzymes deficiencies</i>	Mostly supportive care
<i>PDHc deficiency</i>	
<i>pyruvate carboxylase deficiency</i>	

Screening for treatable IEM in a sick child

- IEM should be considered as a differential diagnosis in acutely ill children:
 - neonates with unexplained, overwhelming, or progressive disease particularly after a normal pregnancy or birth, but deteriorates after feeding
 - children with acute encephalopathy, particularly preceded by vomiting, fever or fasting
 - in children with unexplained symptoms and signs of metabolic acidosis, hypoglycaemia, acute liver failure or Reye-like syndrome
- targeted to pick up treatable diseases in Groups 1 and 2 as early as possible.
- many clues may be gained from a detailed history and physical examination
 - unexplained death among sibling(s) due to sepsis or "SIDS"
 - unexplained disorders in other family members (HELLP (*Haemolytic anaemia, Elevated Liver enzymes, Low Platelet*) syndrome, progressive neurological disease)
 - consanguinity
 - deterioration after a symptom-free interval in a newborn
 - unusual smell - burnt sugar (MSUD), sweaty feet (isovaleric acidemia)
- actively investigate for IEM in any acutely ill child of unknown aetiology, as early as possible during the course of illness. According to the clinical situation, basic and special metabolic investigations must be initiated in parallel.

Table 2. Investigations in children with suspected IEM

Basic metabolic investigations ¹	Special metabolic investigations ¹
ammonia* glucose lactate* blood gases Ketostix (urine)	acylcarnitines (dried blood spot on Guthrie card) amino acids (plasma or serum) ³ organic acids (urine) orotate (urine) - if suspected urea cycle defect <i>[send to the metabolic lab immediately (e.g. by courier) especially when the basic metabolic investigations are abnormal, particularly if there is hyperammonaemia or persistent ketoacidosis]</i>
must be included in work-up of an acutely ill child of unknown aetiology ²	
blood count, electrolytes, ALT, AST, creatine kinase, creatinine, urea, uric acid, coagulation * must send immediately (within 15 minutes) to lab with ice	

Footnote: 1. will pick up most diseases from Group 1 and 2, and some diseases in other groups (which often require more specialized tests)

2. Routine analysis of pyruvate is not indicated

3. Urinary amino acids are the least useful as they reflect urinary threshold. Their true value is only in the diagnosis of specific renal tubular transport disorders (e.g. cystinuria).

Table 3. Useful normal / abnormal values

Basic metabolic tests	Values	Notes
Serum ammonia	<i>Neonates</i> healthy : <110µmol/L sick : up to 180µmol/L suspect IEM : >200µmol/L	1. False elevations are common if blood sample is <i>not analyzed immediately</i> 2. Secondary elevation may occur in severe liver failure
	<i>After the neonatal period</i> normal : 50-80 µmol/L suspect IEM : >100µmol/L	
Anion gap	Calculation $[Na^+] + [K^+] - [Cl^-] - [HCO_3^-]$ normal : 15-20mmol/L	Normal: renal or intestinal loss of HCO ₃ Increased: organic acids, lactate, ketones
Plasma lactate	blood : < 2.4mmol/L CSF : < 2.0mmol/L	False elevations are common due to poor collection or handling techniques

Table 4. "Typical" basic laboratory constellations

Disorders	Ammonia	Glucose	Lactate	pH	Ketonuria	Others
Urea cycle defects	↑↑↑	Normal	Normal	↑	Normal	
Organic acidemias	↑↑	↓, Normal	↑↑	↓↓↓	↑↑↑	↑ anion gap, neutropenia, thrombocytopenia
MSUD	Normal	Normal	Normal	Normal	↓, Normal	
GSD	Normal	↓↓↓	↑↑	↓	Normal	↑ triglyceride, ↑ uric acid, ↑ ALT
FAOD	↑	↓↓↓	↑	↓	↓↓↓	↑ creatine kinase
Mitochondrial disorders	Normal	Normal	↑↑↑	↓↓	Normal	↑ alanine
Tyrosinemia I	Normal	Normal to ↓	Normal	Normal to ↓	Normal	liver failure, ↑ α-fetoprotein, renal Fanconi syndrome

- early contact with the metabolic laboratory will help target investigations, avoid unnecessary tests, and speed up processing of samples and reporting of results

Emergency management of a sick child suspected IEM

In the critically ill and highly suspicious patient, treatment must be started immediately, in parallel with laboratory investigations

This is especially important for Group 1 diseases

Step 1

If the basic metabolic test results and the clinical findings indicate a disorder causing acute endogenous intoxication due to disorder of protein metabolism (Group 1 diseases – UCD, organic acidemias or MSUD), therapy must be intensified even without knowledge of the definitive diagnosis.

Anabolism must be promoted and detoxification measures must be initiated.

- immediately stops protein intake
- reduce catabolism by providing adequate calories
 - 10% glucose infusion, 150ml/kg/day (~60kcal/kg/day), with appropriate electrolytes
 - use commercially available protein-free formula for oral feeding [e.g. Pro-phree® (Ross), Calo-Lipid (ComidaMed®), basic-p (milupa)] if basic metabolic tests are suggestive of disorders of protein metabolism (urea cycle defects, organic acidemias or MSUD)
- add insulin 0.1-1U/kg/hr if blood glucose > 15mmol/L to promote anabolism
- correct hypoglycaemia and metabolic acidosis
- carry out detoxifying measures depending on the laboratory findings
- consult clinical geneticist/metabolic clinician
- supportive/intensive care
 - respiratory insufficiency: provide artificial ventilation
 - septicemia: administer antibiotics
 - seizures: prescribe anticonvulsants
 - cerebral oedema: therapeutic hyperventilation; use mannitol, frusemide; avoid hypotonic fluid overload

Table 4. Specific detoxification measures for hyperammonemia [urea cycle defects]

Therapy	Specifics	Indications
Anti-hyperammonemic drug cocktail	<p><i>Loading dose</i></p> <ul style="list-style-type: none"> - IV sodium benzoate 250mg/kg - IV sodium phenylbutyrate 250mg/kg - IV L-arginine 250mg/kg (mix together in D10% to a total volume of 50mls, infuse over 90 min) <p><i>Maintenance dose</i></p> <p>same dilution as above but infuse over 24 hours</p>	<ul style="list-style-type: none"> • ammonia > 200µmol/L • symptomatic (encephalopathic)
Dialysis	<p>Haemodialysis or haemofiltration, if available</p> <p>If not, peritoneal dialysis is the alternative</p> <p>Exchange transfusion is <i>not effective</i></p> <p><i>(The method of choice depends on local availability and the experience of the medical personnel)</i></p>	<ul style="list-style-type: none"> • ammonia > 400µmol/L • symptomatic (encephalopathic) • inadequate reduction or rising ammonia despite drug cocktail

Table 5. Specific detoxification measures for other IEMs presented as acute intoxication

Disorder	Pharmacological	Non-Pharmacological
Maple syrup urine disease	nil	<p><i>Dialysis</i></p> <p>Indication:</p> <ul style="list-style-type: none"> • plasma leucine >1500 µmol/L • symptomatic (encephalopathic)
Organic acidemias	carnitine 100mg/kg/day	<p><i>Dialysis</i></p> <p>Indication:</p> <ul style="list-style-type: none"> • intractable metabolic acidosis • symptomatic
Tyrosinemia type 1	NTBC 1-2mg/kg/day	none

Abbreviation: NTBC, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3- cyclohexanedione

Step 2

Adaptation and specification of therapy according to the results of the special metabolic investigations/definitive diagnosis.

- specific precursor free amino acids
- natural protein (breast milk or infant formula) is gradually added when child is improving to meet the daily requirement for optimal growth
- oral anti-hyperammonemia drugs cocktail (for urea cycle defects)
- carnitine (for organic acidemias)
- vitamin therapy in vitamin-dependent disorders (e.g. Vit B12-responsive methylmalonic acidemia)
- transfer the child to a metabolic centre for optimisation of therapy
 - plan nutritional management according to child's protein tolerance

Step 3

- be prepared for future decompensation
 - instruction to parents
 - gastrostomy/tube-feeding
 - an emergency letter for the patient detailing the management protocol (usually prepared by metabolic clinician, kept by parents) to use in the event of illness

Table 6. Management considerations in selected disorders

Acute intoxication due to classical galactosaemia

- use a lactose-free infant formula
- send dry blood spots (Guthrie card) for galactose and galactose-1-P uridylyltransferase (GALT) measurement

Disorders with reduced fasting tolerance due to cytoplasmic energy defects (Group 2)

- *acute phase*: 10% glucose infusion, 120- 150ml/kg/day
- *long term*: avoid fasting; take frequent meals, nocturnal continuous feeding, uncooked cornstarch (older children)
(see also approach to hypoglycaemia)

Disorders of mitochondrial energy defects (Group 5)

- *clinical*: suspect in unexplained multi-systemic disorders, especially if involves neuromuscular system
- *laboratory markers*: persistently elevated blood/CSF lactate, plasma alanine
- *diagnosis*: respiratory enzyme assay in muscle biopsy/skin fibroblast, targeted mtDNA mutation study and others
(discuss with metabolic clinician)
- *treatment*: ensure adequate nutrition; treat fever/seizure/epilepsy efficiently, avoid drugs that may inhibit the respiratory chain (e.g. valproate, tetracycline, chloramphenicol and barbiturates)
 - use of vitamins and cofactors is controversial (insufficient evidence)
 - useful website: <http://www.mitosoc.org/>, www.umdf.org/

Management of a asymptomatic newborn but at risk of having IEM

- ideally the diagnosis of treatable IEM should be made *before* a child becomes symptomatic. This may be possible through screening for high risk newborns:
 - a previous child in the family has had an IEM
 - multiple unexplained early neonatal deaths
 - mother has HELLP* syndrome or fatty liver disease in pregnancy

* Haemolysis, Elevated Liver enzymes, Low Platelet syndrome

Role of first-line paediatric doctors

- assist in early diagnosis
- assist initial management, stabilization of patients
- participate in long term care (shared-care with metabolic clinician)
 - rapid action when child is in catabolic stress (febrile illness, surgery etc)
 - adequate hydration and temporary adjustments in nutrition management and pharmacotherapy according to emergency protocol will prevent catastrophic metabolic decompensation

- affected babies may need to be transferred in utero or soon after delivery to a centre with facilities to diagnose and manage IEM
- admit to nursery for observation.
- if potential diagnosis is known: screen for the specific condition e.g. urea cycle disorders – monitor ammonia, plasma amino acid, maple syrup urine disease – monitor plasma leucine (amino acids)
- if potential diagnosis is unknown: Guthrie cards, collect on second day after feeding, mail it immediately and get the result as soon as possible. Other essential laboratory monitoring: ammonia, VBG, blood glucose. Please discuss with the metabolic clinician.

- to prevent decompensation before baby's status is known:
 - provide enough calories (oral/intravenous);
 - may need to restrict protein especially if index case presented very early (during first week of life).
 - protein-free formula should be given initially; small amount of protein (e.g. breast milk) is gradually introduced after 48 hours depending on baby's clinical status.
- if the index patient presented after the first week of life, the new baby should be given the minimum safe level of protein intake from birth (approximately 1.5 g/kg/day). Breast feeding should be allowed under these circumstances with top-up feeds of a low protein formula to minimise catabolism.
- get the metabolic test results as soon as possible to decide whether the baby is affected or not

INVESTIGATING INBORN ERRORS OF METABOLISM (IEM) IN A CHILD WITH CHRONIC SYMPTOMS

Introduction

IEMs may cause variable and chronic disease or organ dysfunction in a child resulting in global developmental delay, epileptic encephalopathy, movement disorders, (cardio)-myopathy or liver disease. Thus it should be considered as an important differential diagnosis in these disorders.

The first priority is to diagnose treatable conditions. However, making diagnosis of non-treatable conditions is also important for prognostication, to help the child find support and services, genetic counselling and prevention, and to provide an end to the diagnostic quest.

Problem 1: Global developmental delay (GDD)

- defined as significant delay in 2 or more developmental domains
- investigation done only after a thorough history and physical examination
- if diagnosis is not apparent after the above, then investigations as in Table 1 may be considered. Even in the absence of abnormalities on history or physical examination, basic screening investigations may identify aetiology in 10-20%.
- in the absence of any other clinical findings or abnormalities in the baseline investigations then further investigations are not indicated.

Table 1. Suggested investigations in children with global developmental delay

Basic screening investigations	
Karyotyping	Metabolic screening using Guthrie card ¹
Serum creatine kinase	Plasma Amino acids ²
Thyroid function test	Urine organic acid ²
Serum uric acid	Neuroimaging ³
Blood Lactate	Fragile X screening (in boys)
Blood ammonia	

Footnote: 1. This minimal metabolic screen should be done in all even in the absence of risk factors

2. This is particularly important if there is one or more of following risk factors: consanguinity, family history of developmental delay, unexplained sibling death, unexplained episodic illness.

3. MRI is more sensitive than CT, with increased yield. It is not a mandatory study and has a higher diagnostic yield when indications exist (e.g. macro/microcephaly; seizure; focal motor findings on neurologic examination such as hemiplegia, nystagmus, optic atrophy; and unusual facial features e.g. hypo/hypertelorism)