When to consider an inborn error of metabolism: an approach to paediatric neurometabolic disorders

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Neurological symptoms are commonly the presenting problem in many inborn errors of metabolism (IEM). It is vital to identify *treatable* conditions early in order to reduce or prevent neurological impairment.

There is limited information available regarding the incidence and prevalence of IEM in South Africa. According to the current available published data, congenital hypothyroidism,[1] galactosaemia[2] and glutaric aciduria type 1[3] are probably the top three treatable conditions. Mitochondrial disorders are an important group of metabolic errors, but remain difficult to diagnose.[4]

This article is intended as a brief guide to key features and available resources and does not deal with specific conditions and management issues.

A clinical approach to IEM with predominant neurological symptoms is discussed below.

Classification

Saudubray *et al.* defined three broad groups of IEM, summarised in Table I.[5,6]

History

The patient's history is an important aspect in the identification of IEM. Key features in the history include:

- pregnancy
  - miscarriages
  - pre-eclampsia, haemolysis, abnormal liver functions, low platelets syndrome (HELLP), associated with disorders of fatty acid beta oxidation
  - abnormal fetal movements
- family history
  - consanguinity
  - siblings with unexplained encephalopathy
  - progressive neurological disorders in family members
- other factors
  - trigger factors, e.g. fasting, exercise, fever, intake of specific foods
  - unexplained 'cerebral palsy'

Clinical presentation

The presentation of IEM changes at different ages; the most important features are summarised below:

Neonatal period

- apnoea
- seizures
- dysmorphology
- hypotonia
- hypoglycaemia
- unexplained jaundice.

Remember

- Sepsis is the most common differential diagnosis
- IEM predisposes to sepsis
- Severe acidosis, hyperammonaemia, organ failure and cerebral oedema are clinical emergencies

Table I. Classification of inborn errors of metabolism according to Saudubray et al.[5,6]

Groups of disorders	Characteristics	Treatment principles

Disorders of intoxication
• Aminoacidopathies (e.g. phenylketonuria)
• Organic acidurias (propionic acidaemia)
• Urea cycle (e.g. ornithine transcarbamylase deficiency)
• Sugar intolerances (galactosaemia)
• Metal intoxication (Menkes, Wilson disease)
	• Accumulation of toxic substances causes symptoms *after a symptom-free period*
	• Fetal development is normal
	• Acute symptoms: vomiting, lethargy, coma, stroke
	• Chronic: failure to thrive, developmental delay, cardiomyopathy
	• Triggers include fever, intercurrent illness or intake of specific foods
	• Recurrent ketosis, acidosis and hyperammonaemia
		• Remove the toxin
		  ◦ Carnitine
		  ◦ Sodium benzoate
		  ◦ Exchange transfusion
		  ◦ Dialysis
		• Special diets
		• Vitamins

Disorders of energy metabolism • Glycolysis • Glycogenosis • Gluconeogenesis • Creatine metabolism • Pentose phosphate pathways • Fatty acid oxidation defects • Mitochondrial disorders	• The clinical spectrum is influenced by the accumulation of toxic compounds and the lack of energy • Multi-organ presentation with wide range of symptoms and signs, e.g. seizures, weakness, ptosis, retinopathy, ataxia, cardiomyopathy, liver failure, Fanconi's syndrome, sensorineural deafness, endocrine or haematological dysfunction • Onset at any age • Stepwise deterioration is typical; in children, there may be transient loss of skills following relatively minor infections • Lactic acidosis is not always present • Non/hypoketotic hypoglycaemia is classic; a suggestive history may include seizures after fasting; cramps post exercise or sudden infant death syndrome	• Avoid fasting hypoglycaemia • Dietary modification • Supplementation with co-factors such as co-enzyme Q10 and carnitine • Management of epilepsy • Specific enzyme replacement therapy (Pompe's) • Monitor disease progression and support where possible – regular ECGs, audiometry
Disorders involving complex molecules Lysosomal disorders Peroxisomal disorders Congenital disorder of glycosylation (CDG) Disorders of cholesterol synthesis	• Symptoms are permanent, progressive and unrelated to food or intercurrent illness	• Enzyme replacement in lysosomal disorders • Chenodeoxycholic acid in cerebrotendinous xanthomatosis

Later presentation
Any unexplained neurological syndrome; static, intermittent or progressive with
- seizures/encephalopathy
- coma
- stroke
- spasticity
- dystonia/rigidity/choreoathetosis
- ataxia
- myopathy/ptosis
- neuropathy
- deafness.

Other organ involvement is common. The central nervous system (CNS) may be secondarily involved, as in galactosaemia.

Investigations
Emergency or baseline investigations usually include:
- full blood count (FBC)
- acid base
- electrolytes
- urea, creatinine
- glucose – if low, ketones, insulin, free fatty acids
- liver functions
- calcium, magnesium
- clotting profile
- urine-reducing substances.

Ammonia and lactate tests are not readily available but are important – contact the nearest tertiary centre if an infant remains acidotic.

Lactate may be falsely elevated in a struggling child or after using a tourniquet. It will be elevated if there is respiratory or hepatic compromise or circulatory disturbance.

Further investigations are best done in consultation with the laboratory or relevant specialist and may include:
- amino and organic acids on blood and urine
- acylcarnitine profiles
- enzyme analyses
- genetic studies
- histology
- imaging.

If advice is not readily available, or the patient is critically ill, heel-prick blood spots on filter paper can be dried, stored frozen (-20°C) and used for future genetic and biochemical testing. Frozen urine, heparinised plasma and EDTA blood samples are useful for analysis. A small sterile skin biopsy in culture medium for fibroblast culture would complete the samples required for further testing.

Treatment
There are potentially treatable disorders where *early* intervention, as for galactosaemia and hypothyroidism, is imperative. Broad neonatal screening is the only way to effectively diagnose these disorders prior to clinical presentation. It is performed routinely in many countries, excluding South Africa. Research is required to delineate which conditions would be most cost effective to screen for in South Africa.

Treatment principles include:
- Treat correctable factors immediately: hypoglycaemia, acidosis, seizures, cardiac failure, hyperammonaemia.
- Start a galactose-free formula if galactose is present in the urine.
- Supplementation with pyridoxine, folinic acid or biotin may be effective for early-onset drug-resistant seizures if there is an underlying defect in any of these pathways.
- Severe hyperammonaemia may require dialysis.

Specific treatment requires the establishment of a diagnosis and a personalised management plan devised by the neurometabolic team, including therapists and a dietician.

Role of the family practitioner
- Recognition of the at-risk infant and appropriate referral.
- Baseline screening.
- Chronic care assistance in liaison with the paediatrician and tertiary care centre or subspecialist.

Role of the paediatrician
- Will vary depending on special interests/area of practice.
- Recognition of the at-risk infant, baseline +/- specific investigations and imaging.
- Stabilisation, management of acute crises in liaison with subspecialist/tertiary centre.
- Referral as necessary for dialysis, intensive care monitoring and subspecialist investigation.
- Chronic care in liaison with subspecialist.

In summary
- If an infant or child's presentation is atypical or unexplained, think of metabolic causes.
- Acute presentation often resembles sepsis, with refractory acidosis, recurrent vomiting, seizures, or altered level of consciousness.
- Chronic presentation is easy to miss and includes failure to thrive, developmental delay, epilepsy, 'cerebral palsy' (especially dystonic), and unexplained intellectual disability.
- Thoroughly check the family history.
- Investigate if there is no clear cause for severe disability.
- The clinical findings are the key to guiding investigations.

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References and further reading available at www.cmej.org.za
Websites for further reading
Acute management protocols for known IEM (UK): http://www.bimdg.org.uk/
Human metabolome database: http://www.hmdb.ca.
IEM protocols (USA): http://newenglandconsortium.org/
Newborn screening: North West University: http://www.newbornscreening.co.za
North West University: http://www.pliem.co.za
SSIEM: http://www.ssiem.org/webresources_inborn.asp
University of Cape Town Chemical Pathology and Metabolic laboratory: http://www.madlab.uct.ac.za

Neurofibromatosis

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The neurocutaneous syndromes are unique for their neurological and cutaneous manifestations.

Neurofibromatosis type 1 (NF1)
Neurofibromatosis type 1 (NF1) is the most common neurocutaneous disorder, with a prevalence of 1 in 3 000 - 4 000 individuals. It is inherited as an autosomal dominant condition and about 50% of cases are new mutations. The gene is located on chromosome 17q11.2 and is a tumour-suppressor gene. This large gene has many different mutations, making routine genetic testing difficult. Prenatal diagnosis is possible but of little prognostic value. There is poor correlation between specific mutations and clinical phenotype, except for deletions of the entire gene where a more severe phenotype and higher numbers of neurofibromas occur. NF1 has variable expressivity and does not run true within a family. NF1 affects all ethnic groups. After the National Institutes of Health (NIH) Consensus Development Conference in 1988, the diagnosis of NF1 has been based on the presence of two or more of the following criteria:
- six or more café au lait spots >5 mm (prepubertal) and >15 mm (post-pubertal) in diameter
- axillary or inguinal freckling