Spectrum of Inherited Metabolic Disorders in Malaysia

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Abstract

Issues pertaining to the diagnosis and management of inborn errors of metabolism (IEM) in Malaysia included low awareness of atypical and variable presentations in IEMs leading to delayed diagnosis or treatment, absence of reliable population data on IEMs and involvement of multiple siblings in the same family due to consanguinity. The importance of careful family history taking and genetic counselling are emphasised. Selected testing of ill infants and children for IEM yielded a positive 2% (264/13,500) results for IEMs in Malaysia. Out of the 264 patients, the spectrum of IEMs in Malaysia included organic acidurias (98), aminoacidopathies (78), urea cycle defects (54), neurotransmitter conditions (12) and lysosomal disorders, mainly mucopolysaccharidosis (14). Confirmatory studies of IEMs are an important aspect of management of IEMs. There is a need for more metabolic specialists and funding for diagnosis and treatment of IEMs in Malaysia. Long-term care issues and cost-effectiveness of IEM therapy, supportive and preventive aspects will need further studies in Malaysia.

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Introduction

Inborn errors of metabolism or inherited metabolic disorders (IEM) are genetic enzyme defects that cause abnormal function of biochemical pathways.[1] When enzyme activity is reduced, the substrate accumulates, causing secondary metabolic effects and deficiency of an essential product of a metabolic pathway, leading to "acute metabolic crisis". Individual case of IEM is rare but collectively, birth prevalence is estimated to be 1 in 3000 to 5000 in the general population. There are a number of anecdotal reports on IEMs in Malaysia.[2-4] However, the actual number of patients with IEMs from population-based studies is not known. In addition, many IEMs which involves "large molecules" or storage disorders with progressive psychomotor regression are often not diagnosed.

Early recognition and treatment of an IEM are important. The child with IEM often deteriorates suddenly and progresses rapidly with severe permanent brain damage. Treatment is effective if started early and the earlier return of metabolic stability correlates well with long-term prognosis and prevents learning handicap. Establishing an accurate diagnosis facilitates genetic counselling for the family, usually before the next child is conceived. Prenatal diagnosis can also be offered as an alternative reproductive option if the genotype or enzyme defect is known.

Patients and Methods

We approach this paper from 2 aspects – qualitative and quantitative aspects. The first aspect relates to the clinical features of IEMs and their diverse presentation. We report on 4 different patients with their respective case histories, highlighting issues related to early diagnosis and management to ensure a better outcome, genetic counselling and long-term care issues in IEMs. For the quantitative aspect, we review the epidemiology and the spectrum of IEMs in Malaysia from the experience of the Specialised Diagnostic Centre, Institute for Medical Research Kuala Lumpur from 1999-2005 in making the diagnosis of IEMs from patients suspected to have IEMs. This will give an indication on the sensitivity of a clinical diagnosis of IEM and to serve as a direction for primary prevention of IEMs in the community.

Findings

Clinical Aspects of IEM in Malaysia

Case 1: A Chinese infant girl presented with lethargy and respiratory distress on the third day of life. The parents were unrelated and there was no significant family history. The perinatal history was uneventful. She was breast-fed and discharged well on the second day of life. Examination showed she was encephalopathic with Kussmaul respiration.

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Investigations showed hypoglycemia with severe ketoacidosis. She was resuscitated and managed in the paediatric intensive care unit as "septicaemia". All microbial cultures were negative. Urine organic acid showed methylmalonic acid >10,000 μmol/mmol, confirming the diagnosis of methylmalonic acidemia. The management included dietary restriction of protein intake via expressed breast milk with energy supplement, carnitine, metronidazole, vitamins C and B12. She was discharged well with no apparent sequelae. Genetic counselling and education of care-givers and other healthcare professionals were provided. Close liaison with the dietician and pharmacist was essential for her care.

Case 2: A 3-year-old Indian girl presented with recurrent admissions of 5 to 6 times per year for vomiting spells and "sleepiness", associated with mild viral illnesses. Her symptoms usually stop when she's put on an IV drip. She had multiple extravasation injuries. The significant dietary history included "self-selected vegetarian diet". The patient disliked "fast food meals" such as fried chicken or burgers. Her mother also admitted that she herself is a vegetarian. The parents are unrelated and the mother had no previous hospitalisation. The patient was admitted for further investigation of "cyclical" vomiting and acute encephalopathy. Investigations showed she had hyperammonemia and the diagnosis of urea cycle defect (partial ornithine transcarbamylase or OTC deficiency) was made based on the clinical picture, the amino acid profile and elevated urinary orotic acid. She was allowed to continue her "self-selected" diet with a special sick regime. She was also treated with ammonium scavenging therapy consisting of oral sodium benzoate and sodium phenylbutyrate. She did not have any more vomiting spells and no further hospital admissions were needed. She had normal developmental milestones.

During the patient's hospitalisation, the mother shared that she was pregnant. After counselling, the parents declined prenatal diagnosis for the pregnancy. There was close liaison with the obstetric team managing the mother's care during the perinatal period. A 3-kg baby boy was delivered at birth. He became symptomatic and rapidly deteriorated. He was treated aggressively in the ICU but succumbed to his illness at 12 weeks of life. The mutation in the OTC gene was successfully identified a year later and the option of prenatal diagnosis was offered to the parents for their next pregnancy.

Case 3: An 8-year-old boy, presented with acute left hemiparesis. He was extensively investigated. The family pedigree was as shown in Figure 1. His mother had short stature, hearing loss and diabetes mellitus. An aunt was also short with diabetes mellitus and an uncle died of status epilepticus. The maternal grandmother had similar medical problems as the mother. A cranial magnetic resonance (MR) imaging showed multiple transient ischaemic sites while a MR spectroscopy showed raised lactate. Mitochondrial DNA study showed: 3243 A>G mutation which confirmed the diagnosis of MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes). He was treated with oral carnitine, coenzyme Q10 and advised to ensure adequate intake of energy, fluids and electrolytes and to avoid drugs that may inhibit the respiratory chain. Genetic counselling and follow-up investigation of family members were arranged.

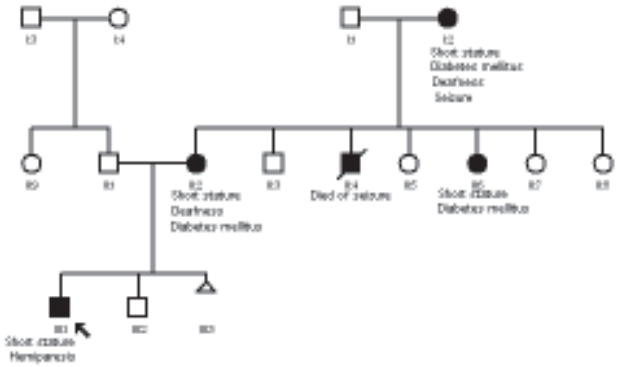

Fig. 1. Family tree of patient with MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes).

Case 4: An 18-year-old boy with Sanfilippo syndrome was admitted for recurrent episodes of seizures. He presented initially with delayed milestones with coarse features at 3 years of age. Urinary screening for mucopolysaccharidosis (MPS) then was negative. He developed developmental regression but no definitive diagnosis was made despite receiving many consultations in the region. A review at 12 years of age by the metabolic service followed by an MPS enzyme study showed deficiency of sulphamidase activity consistent with mucopolysaccharidosis (MPS) type IIIA or Sanfilippo syndrome. He had many on-going issues and these included parental difficulties with medical professionals, recurrent seizures, feeding and behavioural difficulties, psychological and suicidal issues. During this admission, issues such as palliative and transition care were also discussed.

Discussion

A high index of suspicion is required to make a diagnosis of IEM in babies and children. During the neonatal period, the patients are usually well at birth but may develop symptoms the first 2 to 3 days of life after introducing milk feeding. Initial presentations are non-specific and may include poor feeding and lethargy. This progressively worsens with fulminant "septic" presentation.

In older children, the initial presentation may be acute encephalopathy, liver failure or cardiorespiratory shock. This may present for the first time at any age and be associated with a catabolic stress, intercurrent illness and fasting as well as increased protein intake during weaning or "parties". Seizures are usually late presentation of IEM. Progressive coma or central nervous system (CNS) deterioration is usually the presentation. The patient may also present with acidosis and hypoglycemia. The adage "any symptom, any organ, any age!" is important to remember in IEMs. In addition, many other common conditions in Malaysia e.g. cerebral malaria, dengue shock syndrome and acute infective hepatitis may resemble IEMs.

In an acute metabolic crisis, aggressive resuscitation and ICU care are mandatory. Working closely together with paediatric intensivists, anaesthesiologists or neonatologists, this includes correction of dehydration, shock and provision of adequate cardiorespiratory support and prevention of cerebral oedema. Empiric treatment with intravenous antibiotics, prevention of hypoglycaemia and hypothermia and correction of acidosis and hyperammonemia are required. Consultation with IEM laboratory staff and physician with metabolic expertise are essential.

Proper collection and transportation of urine and blood samples are the most important steps in the diagnosis of IEM. Samples must be obtained during the acute crisis preferably before the therapy commenced. Investigations done after metabolic stability has been achieved may give inconclusive or false negative results. Samples must be transported to the laboratory as soon as possible. The investigations of suspected acute IEM usually show one or more of these tests outcome being out of proportion to the clinical state of the child's condition. Besides the usual full blood count, blood urea and serum electrolytes, serum creatinine and liver function test, other basic investigations in suspected acute metabolic crises include blood gas and acid-base balance, plasma glucose, plasma ammonium, serum lactate and urine ketone, reducing substances & pH. Plasma amino acid and urine organic acid assays will point to common IEMs. Once metabolic stability and IEM diagnosis were made, joint management with a dietician or nutritionist experienced in IEM is mandatory. Specific dietary manipulation, example, metabolic foods for substrate limitations and specific pharmacotherapeutic agents may be required.[16,17]

Detailed family history and genetic counselling are essential. In many families, consanguinity may be an important issue. In Malaysia, it may be common to see 2 or more siblings affected by the same IEM. This may be related to acceptance of consanguineous marriages in some Asian cultures and also the delay in making a correct diagnosis before the next sibling is conceived or born. Long-term care issues in IEM include the delayed diagnosis of lysosomal conditions causing chronic neuropathic diseases and significant morbidity. Issues such as transition care for storage diseases and palliative care for neurodegenerative conditions must be discussed. Recently, many other modalities of treatment have emerged. These include stem cell transplantation and enzyme replacement therapy for lysosomal diseases. The cost-effectiveness of caring for patients with IEMs is being debated. Should there be further investments in setting up intensive care unit and training of medical practitioners in the early recognition of acute metabolic crises or will funds be better spent in an expanded newborn screening for IEMs?

Epidemiology and Spectrum of IEMs in Malaysia

Over a 6-year period from 1999 to 2005, a total of 13,400 samples were received nationwide from medical practitioners consisting mainly of paediatricians by the Specialised Diagnostic Centre, Institute for Medical Research Kuala Lumpur. These samples were obtained from infants and children who were suspected to have IEMs based on their clinical presentation such as poor feeding and vomiting, cardiorespiratory collapse, hyperammonemia, unexplained metabolic acidosis, recurrent "sepsis", acute encephalopathy and seizures. Other indications included psychomotor retardation, developmental regression and dysmorphic features. In 1998 when the service was first started, amino acid analysis of body fluid samples were processed and derivatised with PITC and 8 ul of the mixture was injected into the JASCO HPLC system using gradient pump and reversed-phase column heated at 40°C. The ultra-violet detector was set at 254 nm, and run for 80 minutes.[5] In 2003, the method was later change to fully automated amino acids analyzer (Biochrome 30+) with post-column derivatisation with ninhydrin. Plasma total homocysteine was analysed using HPLC and Bio-Rad Homocysteine kit. Patients with moderate degree of hyperphenylalaninemia and positive clinical symptoms were sent to overseas laboratory to confirm the diagnosis of pterins disorders. Random urine for organic acids was performed by GC-MS system from Hewlett Packard, USA after organic solvent extraction and derivatisation of organic acids with BSTFA.[6,7] Diagnosis of mucopolysaccharidosis was made whereby urine glycosaminoglycan was quantified using dimethyl-methylene blue and was later characterised using high resolution electrophoresis by method described by Hopwood.[8] Diagnosis of peroxisomal disorders was made by analyzing plasma samples for very long chain fatty acids (VLCFA) and phytanic acids. This was processed using a method described by Moser and Moser.[9] The specific

Table 1. Inborn Errors of Metabolism, Institute for Medical Research (1999-2005)

I	**Organic aciduria: 98**	
1.	Methylmalonic aciduria	41
2.	Glutaric aciduria type 1	19
3.	Isovaleric aciduria	13
4.	Propionic aciduria	8
5.	3-OH isobutyric aciduria	8
6.	Ethylmalonic encephalopathy	4
7.	Others	5
II	**Aminoacidopathy: 78**	
1.	Maple Syrup Urine Disease	44
2.	Non-ketotic hyperglycinemia	16
3.	Classical phenylketonuria	7
4.	Homocystinuria	6
5.	Tyrosinemia	5
III	**Urea cycle defect: 54**	
1.	Arginosuccinic aciduria	15
2.	Citrullinemia	11
3.	Partial ornithine transcarbamylase (OTC) deficiency	11
4.	Ornithine transcarbamylase deficiency	5
5.	N-acetylglutamate synthase (NAGS) deficiency	6
6.	Carbamylphosphate synthase 1 (CPS 1) deficiency	3
7.	Arginase	3
IV.	**Neurotransmitter: 12**	
1.	Tetrahydrobiopterin deficiency	9
2.	Aromatic L-amino acid decarboxylase deficiency	3
V.	**Lysosomal: 14**	
1.	Mucopolysaccharidosis	11
2.	I cell disease	3
VI.	**Others: 8**	
1.	Glutaric aciduria type II	4
2.	3-hydroxy-3-methylglutaryl (HMG) CoA lyase deficiency	3
3.	Citrin deficiency	1
	Total	**264**
	Positive IEMs: 264/13,400	**2%**

diagnosis of peroxisomal disorders could not be made as this will require enzyme assays.

The results of the analysis are shown in Table 1. An average of 2200 samples from patients were analysed a year. The yield from this cohort was 2% (264/13,400). On the basis of clinical suspicion for IEMs, the yield of 2% positive diagnosis of IEMs is a useful baseline. This is in keeping with some studies.[10,11] However, this may be an indication that some of the tests may not be required. In addition, there were 5 cases with peroxisomal disorders. This and some of the other IEMs will require confirmatory studies such as enzyme assays and molecular genetic testing. The diagnosis of fatty acid oxidation defects cannot be reliably made based on organic acid analysis. Nevertheless, the delineation of the spectrum of inherited metabolic disorders is important as it added new information to the current knowledge of IEMs in Malaysia.[12-15,17] However, further studies are required to confirm these findings. Currently, a pilot study of an expanded newborn screening programme in selected public hospitals is ongoing.

Conclusion

We reported that selective IEM testing in ill infants and children yielded 2% positive results for IEM in Malaysian paediatric practice. Issues pertaining to the diagnosis and management of IEM in Malaysia included low awareness of atypical and variable presentations in IEMs leading to delayed diagnosis or treatment, absence of reliable population data on IEMs and involvement of multiple siblings in the same family due to consanguinity. The importance of careful family history taking and genetic counselling are emphasised. Confirmatory studies of IEMs are an important aspect of management of IEMs. More resources are needed to address the morbidity and mortality related to IEM in Malaysia. Long-term care issues and cost-effectiveness of IEM therapy, supportive and preventive aspects will need further studies and debate.

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