To Err is Genetics: Diagnosis and Management of Inborn Errors of Metabolism (IEM)

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INTRODUCTION

The term inborn errors of metabolism (IEM) was coined by Dr A.E. Garrod in 1908 for disorders that are caused by a deficiency of enzyme catalysis or an enzyme that facilitates the transport of biological substances across membranes (Ann, 1988; Velazquez et al. 2000; Ward, 1990).

Frequency

The frequencies for each individual IEM vary, most are very rare but collectively they are very common.

The frequency for each individual disease is decided by the geographical and ethnic composition of the population. The incidence within different geographical regions and ethnic groups varies with predominance of certain IEMs within particular groups (e.g. cystic fibrosis, 1 per 1600 people of European descent; sickle cell anemia, 1 per 600 people of African descent; Tay Sachs disease is found in 1: 3500 Ashkenazi Jews).

In the US, the incidence, collectively, is estimated to be between 1 in 1400 and 1 in 5000 live births.

A study by Wilken et al. (2003) in an Australian cohort, screened with tandem mass spectrometry, the prevalence of inborn errors, excluding phenylketonuria, was 15.7 per 100,000 births (95 percent confidence interval, 11.9 to 20.4).

Yoon et al. (2005) screened 79,179 newborns (from April 2001 to March 2004) for organic, amino and fatty acid metabolism disorders, which account for approximately 5.4% of annual births in South Korea. Twenty-eight newborns were diagnosed with one of the metabolic disorders and the collective estimated prevalence amounted to 1 in 2800 with a sensitivity of 97.67%, a specificity of 99.28%, a recall rate of 0.05%, and a positive predictive value of 6.38%.

In Japan, the incidence of histidinemia, phenylketonuria, galactosemia and homocystinuria were found to be 140, 16, 14 and 7 in 1 million live births, respectively (Yasuda, 1984).

In British Columbia, Canada, approximately 24 children per 100 000 births (~60% of the total disease groups surveyed) have a disease involving amino acids (including PKU), organic acids, primary lactic acidosis, galactosemia, or a urea cycle disease. Approximately 2.3 children per 100 000 births (~5%) have some form of glycogen storage disease. Approximately 8 per 100 000 births (20%) have a lysosomal storage disease; ~3 per 100 000 births (7%-8%) have a respiratory chain-based, mitochondrial disease and ~3 to 4 per 100 000 (7%-8%) of births have a peroxisomal disease (Applegarth et al., 2000).

The incidence of IBEM in Thailand is yet unknown, however, by estimation it is generally accepted to be 1 in 5,000 (Wasant, 1995).

In Saudi Arabia, out of 26063 screened, the total number of organic acidemias and amino acid disorders identified were 259 and 124 respectively (Ozand, 1998).

In India, 24 million newborns are born each year; 780,000 are born with congenital malformation, 340,000 with G6PD, 20,800 with metabolic disorder, 21,000 with Down syndrome, 10,400 with congenital hypothyroidism, 9000 with thalassemia and 5200 with sickle cell anemia. In a hospital based study in India biochemical screening of 4400 cases of mental retardation revealed that 5.75 % (256 cases) were due to a metabolic disorder (Kumta, 2005).

Mortality/Morbidity

IEMs can affect any organ system and usually do affect multiple organ systems. Manifestations vary from those of acute life-threatening disease to subacute progressive degenerative disorder. Progression may be unrelenting with rapid life-threatening deterioration over hours, episodic with intermittent decompensations and asymptomatic intervals, or insidious with slow degeneration over decades.

Pattern of Inheritance

The mode of inheritance determines the male-to-female ratio of affected individuals. Many

Table 1: The frequency of inherited metabolic disorders in UK (adapted from Sanderson et al. 2006).

Condition	*Total number of cases*	*Birth Prevalence live births*	*Upper 95% ci*	*Lower 95% ci*
PKU[1]	25	1 in 12420	5008	33784
Amino acid (excluding PKU)	58	1 in 5354	2943	9990
Urea cycle defects	14	1 in 22179	6702	90909
Carbohydrate	19	1 in 164	4509	52910
Organic acid	39	1 in 7962	3837	17301
Glycogen storage	21	1 in 786	5504	44643
Lysosomal stroage	60	1 in 5175	2874	9551
Purine and pyrimidine[2]	4	1 in 77628	12063	2000000
Fatty acid oxidation	24	1 in 12938	5123	35971
Peroxisomal	23	1 in 13500	5244	38462
Mitochondiral	63	1 in 4929	2776	8953
Metals[3]	11	1 in 28228	7418	147059
Lipids and steroids[4]	20	1 in 15526	5647	48544
Porphyrin and haem[2]	1	1 in 310510	10070	3333333
Miscellaneous	14	1 in 22179	6702	90909
Total (including PKU)	396	1 in 784	619	970

[1]Date included from the Neonatal Screening Programme
[2]Incomplete as diagnosis usuall made in supra-regional centres
[3]Incomplete as some diagnoses will be made in non-specialist labs
[4]Only includes steroid sulphatase disorders and Smith-Lemli-Opitz syndrome

Table 2: Prevalence of inherited metabolic disorders in Heidelberg, Germany (adapted from Baric et al. 2001).

Inborn error[b]	*Positve*	*Prevalence*	*Recall rate (%)*
PKU/MHP	23/28	1:5,774	0.06
MSUD	2	1:107,000	
NKH	2	1:107,000	
UCD	1		
MCAD	15	1:14,266	0.04
SCAD	6	1:36,000	
VLCAD	1	1:70,000	
CPT I, II, SCD	3	1:70,000	
IVA	3	1:70,000	
MMA/Cb	2	1:107,000	0.14
GA 1	3	1:70,000	
3-MCC	4	1:43,000	
Overall	103	1:2,077	0.30

[a]The number of samples analyzed was 214,000
[b]PKU/MHP-phenylketonuria/mild hyperphenylalanni-nemia; MSUD
-maple syrup urine disease; NKH-nonketotic hyperglycinemia;
UCD-urea cycle discorders; MCAD-medium-chain acyl-CoA
dehydrogenase deficiency; SCAD-short-chain acyl-CoA
dehydrogenase deficiency; VLCAD-very long-chain acyl-CoA
dehydrogenase deficiency; CPT I, II, SCD -camitine
palmitoyltranspherase deficiency type I, carnitine
palmitoyltranspherase deficiency type II, systemic carnitine
deficiency; IVA - isolvaleric acidemia; MMA/Cbl-methylmalonic
acidemia/cobalamin deficiency; GA 1- glutaric acidemia type 1;
3-MCC-3-methylcrotonyl-CoA carboxylase deficiency.

IEMs have multiple forms that differ in their mode of inheritance. The male-to-female ratio is 1: 1 for autosomal dominant and autosomal recessive. It is also 1: 1 for X-linked dominant if transmission is from mother to child.

Age

Age for presentation of clinical symptoms varies for individual IEM and variant forms within the IEM. The timing of presentation depends on significant accumulation of toxic metabolites or on the deficiency of substrate.

The onset and severity may be exacerbated by environmental factors, such as diet and intercurrent illness. Disorders of carbohydrate or protein metabolism and disorders of energy production tend to present in the neonatal period or early infancy and tend to be unrelenting and rapidly progressive. Less severe variants of these diseases usually present later in infancy or childhood and tend to be episodic. Fatty acid oxidation, glycogen storage, and lysosomal storage disorders tend to present insidiously in infancy or childhood. Disorders manifested by subtle neurologic or psychiatric features often go undiagnosed until adulthood.

Pathophysiology

Single gene defects result in abnormalities in

the synthesis or catabolism of proteins, carbohydrates, or fats. Most are due to a defect in an enzyme or transport protein, which results in a disruption in a metabolic pathway. This may result in toxic accumulations of substrates before the disruption, intermediates from alternative metabolic pathways, and/or defects in energy production and utilization caused by a deficiency of products beyond the point of disruption. Nearly every metabolic disease has several forms that vary in age of onset, clinical severity and, often, mode of inheritance.

CLASSIFICATION

IEMs can be simply categorized as follows:

- Disorders of protein metabolism (e.g, amino acidopathies, organic acidopathies, and urea cycle defects)
- Disorders of carbohydrate metabolism (eg, carbohydrate intolerance disorders, glycogen storage disorders, disorders of gluconeogenesis and glycogenolysis)
- Lysosomal storage disorders
- Fatty acid oxidation defects
- Mitochondrial disorders
- Peroxisomal disorders

A detailed and widely used classification of IEMs is found in The Metabolic and Molecular Basis of Inherited Disease, 1995 edition, by Saudubray and Cherpentier that categorizes IEM according to clinical phenotype. Figure 1 shows a summary of the classification.

Group 1

It involves cellular organelles and includes lysosomal, peroxisomal, glycosylation, and cholesterol synthesis defects. Among these, some lysosomal disorders can be efficiently treated by enzyme replacement or substrate reduction therapies.

Group 2

It includes inborn errors of intermediary metabolism that give rise to an acute or chronic intoxication. It encompasses aminoacidopathies, organic acidurias, urea cycle disorders, sugar intolerances, metal disorders and porphyrias. Clinical expression can be acute or systemic or can involve a specific organ, and can strike in the neonatal period or later and intermittently from infancy to late adulthood. Most of these disorders are treatable and require the emergency removal of the toxin by special diets, extracorporeal procedures, cleansing drugs or vitamins.

Group 3

It includes inborn errors of intermediary metabolism that affect the cytoplasmic and mitochondrial energetic processes. Cytoplasmic defects encompass those affecting glycolysis, glycogenosis, gluconeogenesis, hyperinsulinisms, and creatine and pentose phosphate pathways; the latter are untreatable. Mitochondrial defects include respiratory chain disorders, and Krebs cycle and pyruvate oxidation defects, mostly untreatable, and disorders of fatty acid oxidation and ketone bodies that are treatable.

Clinical Manifestation

In neonates and children are nonspecific and include poor feeding, vomiting, dehydration, lethargy, hypotonia and seizures. These features are very similar to that of septicemia, a major reason why IEMs go undetected (Burton, 1987; Goodman, 1986).

Among other clinical findings, there are descriptions of dysmorphic features present at birth (generally when fetal energy is affected), or developed during the first year of life as in lysosomal diseases.

In adults, the symptoms may include mild-to-profound mental retardation, autism, learning disorders, behavioral disturbances, muscle weakness, progressive paraparesis, hemiparesis, dystonia, chorea, ataxia, ophthalmoplegia, visual deficit, epileptic crisis, hepato-splenomegaly and hypoglycemia (Scharz and Wendel, 2005).

Some manifestations may be intermittent, precipitated by the stress of illness, or progressive, with worsening over time.

DIAGNOSIS AND MANAGEMENT

There are 5 important steps in the diagnosis and management of an IEM. (Burton, 1987; Goodman, 1986; Ogier et al., 1995).

I. Suspicion

An important key to diagnosing an IEM is thinking about the possibility in the first place.

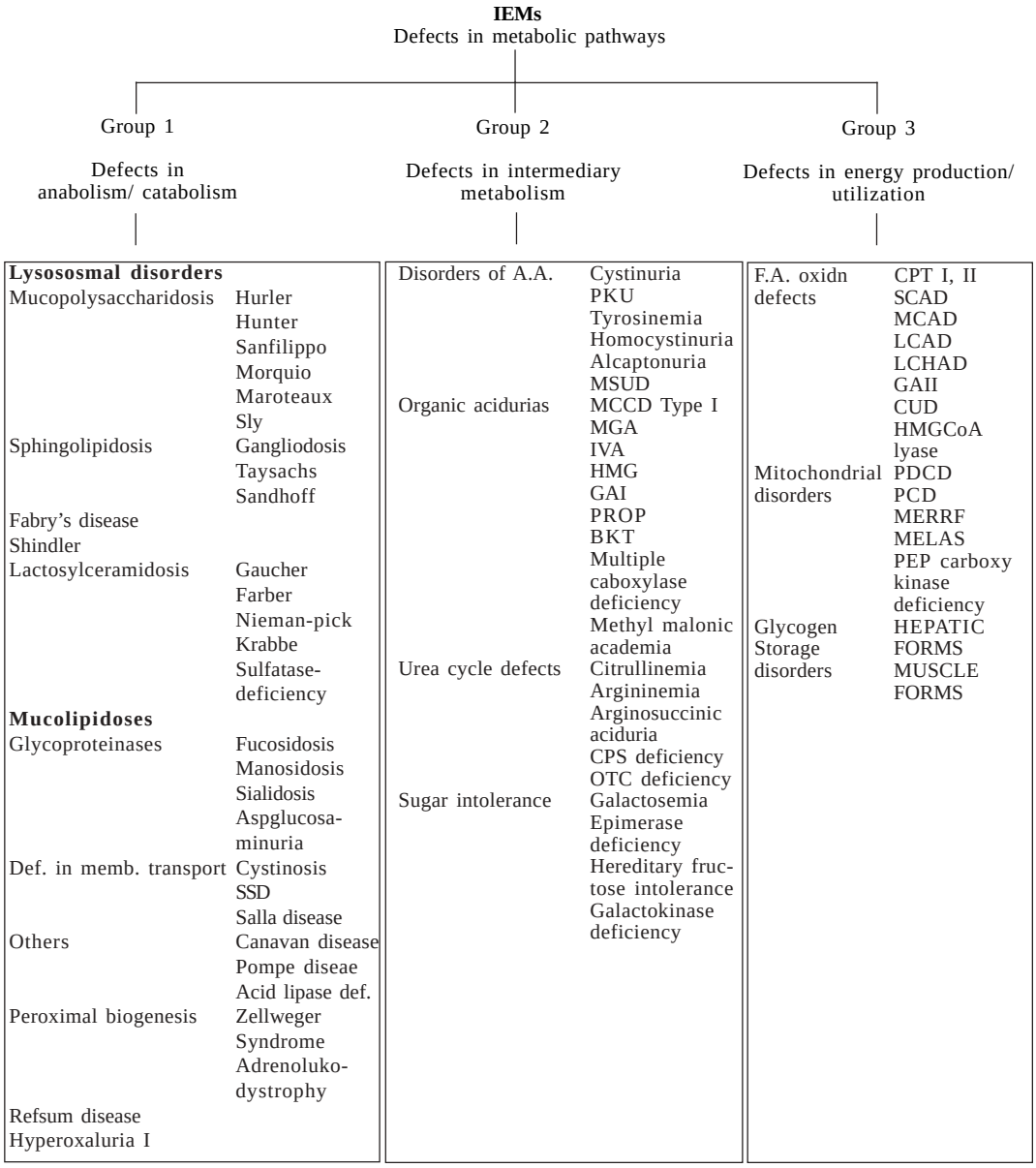

Fig 1. Clinical classification of IEMs adapted from Saudubray and Cherpentier, 1995. methylglutaconic academia (MGA), carbamoyl phosphate synthetase deficiency (CPS), Ornithine transcarbamylase deficiency (OTC), Maple syrup urine disease (MSUD),Methyl crotonyl-coA carboxylase deficiency, Methyl glutaconic academia (MGA), Hydroxy-3-methyl glutaric academia, propionic academia(PROP), Isovaleric academia (IVA), Glutaric academia(GA), Carnitine palmityl transferase deficiency (CPT), Carnitine uptake deficiency(CUD), Short chain acylcoA dehydrogenase deficiency (SCAD), pyruvate dehydrogenase complex deficiency (PDCD)pyruvate carboxylase deficiency(PCD),

The symptoms and signs for an IEM are very common and nonspecific, therefore one should think of IEM as an etiology in unexplained/ peculiar cases and try to rule out the possibility. Few clues are listed in Table 3, those are suggestive of an IEM.

II. Evaluation

Once the possibility of an IEM is suspected, how should it be evaluated? There are 4 parts to the evaluation of an IEM:

Table 3: Clues suggesting an inborn error of metabolism

Positive family history	*Consanguinity*
Failure to thrive	Vomiting/or Diarrhoea
Develpomental delay	Hepato/or Splenomegaly
Seizures	Respiratory distress/or apnea
Jaundice	Unusual odor
Grotesque facial features	Abnormal hair
Macroglossia	Abnormal eye findings
Frequent infections	Myopathy
Progressive paraparesis	Hemiparesis
Chorea	Ataxia
Dystonia	Behavioral disturbance

A. History, Family History

The history largely focuses around the features that arouse suspicion for an IEM. One of the most important clue is a history of deterioration after an initial period of apparent good health ranging from hours to weeks.

Developmental delay, particularly missing milestones. Another key feature is change in the diet and unusual dietary preferences particularly protein or carbohydrate aversion

The family history is very important but often not taken. Most IEM are autosomal recessive, so there may have been siblings with similar illnesses or deaths from “sepsis” or “SIDS”. The parents may be consanguineous or come from a genetic isolate. There are also X-linked, and mitochondrial inherited IEM, so a family history must include information about the mother’s siblings, their children, etc. A pedigree only containing nuclear family members is inadequate; therefore a detailed and complete pedigree should be recorded.

B. Physical Examination

The physical exam of patients with IEM is usually normal except for nonspecific findings such as lethargy, coma, apnea or hyperpnea, seizures, hypotonia, etc. Physical findings that are important and will help to narrow the differential diagnosis include: facial dysmorphism, cataracts, retinopathy, structural brain anomalies, hypertrophic or dilated cardiomyopathy, hepatomegaly, multicystic dysplastic kidneys and myopathy.

C. Initial Screening Tests

The initial evaluation suggested in the literature varies in relation to the number and type of tests and it is generally accomplished in a progressive way, according to the results obtained. The investigation of an IEM should begin with simple urine and blood analysis. The first step is checking for unusual odors in urine, which can be particularly helpful in several disorders

Urine tests (Table 4) are of great importance in countries and labs where higher technical sophistication is not available. Some of them are not specific, but still a positive result can direct the investigator towards one or more specific tests.

The blood test is the second step towards identifying an IEM. Blood tests encompass complete blood count, blood gases and blood

Table 4: Urinary odor in IEMs

Disorder	*Odor*	*Compound*
Phenylketonuria	Musty	Phenyl acetate
Tyrosinemia	Cabbage	Hydroxy butyric acid
	Rancid butter	Oxomethiol butric acid
Maple syrup urine disease	Maple syrup	Oxoisocaproic acid
	Burnt Sugar	Oxo methyl valeric acid
isovaleric acidemia, glutaric acidemia type II	sweaty feet	isovaleric acid
Methylcrotonyl CoA carboxylase	Cat urine	Hydroxy isovaleric acid
multiple carboxylase deficiency	Cat urine	Hydroxy isovaleric acid
Methylmalonic academia	Acid smell	Methylmalonic acid
Cystinuria	Sulfurus	Hydrogen sulfide
Hydroxy methyl glutaric acidurias	Cheese	

Table 5: Urine tests to IEMs

Benedict	Galactosemia, fructose intolerances, alkaptonuria. Lowe syndrome. Positive also for diabietes mellitus, tenal glycosuria. Fanconi syndrome, lactase deficiency, pentosuria, vitamin C excessive ingestion, sulfonamides, leucacyline chloramphemcol and pamino salicylic acid
Ferric chloude	Phenyikelanutia, tylosenimia, hisdinemia, maple syrup urine disease, hyperglycinemia, alkaptonuria. Positive also for pleochromocytoma, carcinomatosis, hepatic cirrhasis, transitory tyrosinemia, conjugated hyperbilirubinria, L-dopa metabolites, pyruvic acidosis. salicylates, acetoacetic acid, phenothiazines, methionine malabsorption, melanoma, lactic acidosis and isoniazide excretion
Dinitrophenyihydrazine	Phenylketonuria, maple syrupurine disease, histidinemia, methioninemalabsorption, hyperglysinemia, glycogen storage diseases I, III, V and VI, lactic acidosis and pyruvic acidosis.
Nitrosonaphthol	Hereditary tyrosinemia, transitory lyrosenemia, liver disease, fructosemia and galactosemia
p-itroandine	Methylmalonic acidurra
Cima bromide	Mucopalysaccharidoses Positive also for Marfan syndrome, arthritis thoumatod, cretinism and carcinomatosis
Cyanida-nitroprusside	Homocystinuria, cystinuria
Nitroprusside silver*	Homocystinuria, cystinuria
Toluidine blue spot test*	Mucopolysaccharidoses. Positive also for Marfan syndrome, rheumaloid arthritis. critimsm and carcinomatosis.
Erirch*	Porphyria
Paper chromatography	Disorders of amino acids

* These are not part of the minimum screening but they should be done for confirmation as complementary tests, of in specific cases such as porphyria.

electrolytes (Na, K, Cl, P, Ca). The panel of tests should also include lactate, liver function test, cholesterol, pyruvate, urea, creatinine and uric acid.

A low neutrophil count may be indicative of organic acidemias. The lactate/pyruvate ratio of less than 25 cancels the possibility of lactic acidosis, organic acidurias, urea cycle defects and fatty acid metabolism. High levels of lactate and pyruvate are symbolic of mitochondrial defects (Cleary and Green, 2000). An elevated ammonia level in blood points to urea cycle abnormalities and some organic acidemias. Serum and urine amino acid analyses reveal hyperalaninemia. A value above 16 for the Anion Gap is suggestive of organic acidurias. Glucose level is checked to rule out hypoglycemia, which is a common feature of many IEMs.

Utmost care should be taken while performing these tests, as they are notoriously sensitive to artifactual sampling or handling errors making the results worthless.

D. Advanced Screening Tests

There are numerous other biomarkers that are used in many laboratories that specialize in biochemical genetics (Lepage et al. 2006). These include carnitine, acylcarnitines, very long chain fatty acids, lysosomal enzymes, etc. These tests are key to exclusion or inclusion of an IEM; therefore appropriate age-related references intervals are crucial.

Magnetic resonance imaging (MRI) with greater sensitivity to small changes in the water content of brain tissue, to changes in the binding of free water (revealed by magnetization transfer), and to the extent and anisotropy of water diffusion (revealed by diffusion imaging) has cast new light on very complex and important molecules. Barkovich (2000) has very comprehensively reviewed the nature of myelin and the effect of its different components on MR imaging parameters that may help to understand and diagnose inborn errors of metabolism better.

Magnetic resonance spectroscopy (MRS)- of the brain shows high lactate levels in individuals with mitochondrial disorders (Barkowich et al. 1993; Linn et al., 1993). A study by Engelke et al. (2004) showed that (1) H-NMR spectroscopy may also be used to identify and quantify N-acetylated metabolites in urine for diagnosing inborn errors of metabolism.

Tandem MS can be considered as the most important of the new technologies for newborn screening for inborn errors of metabolism (Clarke, 2002). It has the potential for simultaneous multi-disease screening for selected disorders of amino acid and organic acid metabolism using a single analytical technique and is complementary to immunoassay-based methods for congenital

hypothyroidism (CH) and CAH screening. The technology has been demonstrated to be robust (accurate, sensitive, lack of false positives) and suitable for the reliable detection of PKU and some other inborn errors of metabolism (Chase et al. 2005).

III. Treatment

The basic principle for treatment of the acute inborn errors is reduction of the substrate that accumulates due to catabolic enzyme deficiency. This can be mediated by an increasing number of therapeutic approaches:

1. Prevent Catabolism: Administration of calories is used in the treatment of acute episodes to try to slow down catabolism. A poor intake of calories can contribute to poor metabolic control just as much as an excessive intake of the offending substance.

2. Limit the Intake of the Offending Substance: Simple restriction of certain dietary components such as galactose and fructose form the basis of treatment in galactosaemia and fructose intolerance (Yu and Wong, 1986). Neonates with PKU should be given a protein substitute that is phenylalanine-free

3. Increase Excretion of Toxic Metabolites: Rapid removal of toxic metabolites can be achieved by exchange transfusion, peritoneal dialysis (PD), haemodialysis, forced diuresis, using alternative pathways for the excretion of toxic metabolites (Low, 1996). For example, carnitine is useful in the elimination of organic acids in the form of carnitine esters. Sodium benzoate and phenylacetate are useful in treating hyperammonemia.

4. Enzyme Replacement Therapy: Studies by Van den Hout et al. (2004) show that Human alpha glucosidase enzyme is safe and effective in pompe's disease. Laronidase (Aldurazyme) enzyme replacement therapy has been developed as a treatment strategy for MPS I patients and has been approved for clinical practice (Wraith et al., 2005). Desnick and Banikazemi (2006) have shown that Fabry-specific enzyme replacement therapy (ERT) with recombinant alpha-Gal A (Fabrazyme) is safe and effective. Wenstrup et al, (2007) showed that ERT with Imiglucerase significantly improves BMD in patients with Gaucher disease.

5. Increase the Residual Enzyme Activity (if Possible): This is usually accomplished by administration of pharmacologic doses of the vitamin cofactor for the defective enzyme. If the binding constant for the vitamin has been altered and the enzyme is otherwise reasonably functional, increasing the vitamin concentration will increase enzyme activity via a mass action effect. A study by Miller et al. (2002) showed that B12 decreases the urinary levels of methyl malonate by enhancing activity of Trans CobalminII. A comprehensive analysis of the enzyme deficiency and the cofactor needed can be found at www.vrp.com/art/1902.asp?c=1171549417093 andk=/det/9843.aspandm=/andp=noands=0 - 32k

6. Reduce Substrate Synthesis: Inhibition of substrate synthesis has been used as a strategy for treating glycolipid lysosomal storage disease. In this disorder glycohydrolase that catalyzes glycosphingolipid (GSL) is defective leading to accumulation of GSL in lysosome and precipitation of the disease. This approach uses imino sugar N-butyldeoxynojirimycin (NB-DNJ) to balance the rate of (GSL) synthesis with the impaired rate of GSL breakdown. This inhibits the first step in GSL synthesis (Platt et al., 2001).

7. Replacement of the End Product: Another aspect in the management of IEM is the replacement of a product due to an enzyme defect. In patients with glycogen storage disease, deficient hepatic glucose output leads to hypoglycaemia. Hypoglycaemia can be prevented by frequent feeds during the day and continuous nasogastric feeding at night, in infancy and early childhood. Raw cornstarch (2 g/kg every six hours) has been shown to be effective in preventing hypoglycaemia in older children with glycogen storage disease type I as well as decreasing the hyperlipidaemia, hyperuricaemia, and lactic acidaemia (Chen et al., 1984).

8. Transplantation and Gene Therapy: For he last 25 years, haematopoietic cell transplantation (HCT) has been used as effective therapy for selected inborn errors of metabolism (IEMs), mainly lysosomal storage diseases and peroxisomal disorders. The main rational for HCT in IEMs is based on the provision of correcting enzymes by donor cells within and outside the blood compartment (Boelans, 2006; Cox et al., 2006).

CONCLUSION

The commonest mistake made in the management of an IEM is *delayed diagnosis* or *misdiagnosis*. It is important for paediatricians and

neonatologists to keep in mind inborn errors of metabolism as a cause of illness in the neonatal period. In unexplained cases, the possibility of an IEM should be entertained, as early as possible, as many disorders are treatable and, in most cases, successful outcome is dependent on a rapid diagnosis and early instigation of therapy. Even with untreatable disorders, it is important to establish the diagnosis in the index case in order to allow prenatal diagnosis in subsequent pregnancies.

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of inborn errors of metabolism and the laboratory studies necessary to arrive at an initial diagnosis. The aim of this review is to demystify this elusive and extremely heterogeneous group of diseases, to promote clinical vigilance in their detection, and to provide a systematic approach to diagnosis when clinical suspicion is aroused.

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ABSTRACT The colossal number and kaleidoscopic clinical presentation of inborn errors of metabolism present an indomitable task to a clinician. Prevention of death or permanent neurological sequelae in patients with these disorders is dependent on early diagnosis and institution of appropriate therapy. It is therefore necessary for the pediatrician to be familiar with the major signs and symptoms of inborn errors of metabolism and the laboratory studies necessary to arrive at an initial diagnosis. The aim of this review is to demystify this elusive and extremely heterogeneous group of diseases, to promote clinical vigilance in their detection, and to provide a systematic approach to diagnosis when clinical suspicion is aroused.

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