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REVIEW ARTICLE

INBORN ERRORS OF METABOLISM: REVIEW AND DATA FROM A TERTIARY CARE CENTER

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ABSTRACT

Inherited metabolic disorders are a heterogeneous group of genetic conditions mostly occurring in childhood. They are individually rare but collectively numerous, causing substantial morbidity and mortality. We have retrospectively reviewed a total of eight hundred and sixty nine cases with different age groups that had been referred from several diagnostic centers and hospitals of India to the Department of Metabolism in Narayana Hrudayalaya, as cases suspected with inborn errors of metabolism. Advanced techniques applied were to diagnose the disorders of inborn errors of metabolism. Data analyzed indicates occurrence of several metabolic disorders in our population. The need to screen for an inborn error of metabolism arises out of the fact that most cases take to irreversible effects as time progress. Emphasis has to be laid on early detection and prompt management, which could help in alleviating symptoms and preventing complications and consequent incapacitation.

KEY WORDS

Inborn errors of metabolism, Aminoacidopathies, Organic acidemia, Carbohydrate metabolic defect.

INTRODUCTION

Inborn errors of metabolism (IEM) individually are rare but collectively are common. In IEMs single gene defects are responsible for the abnormalities in the synthesis or catabolism of proteins, carbohydrates or fats by way of defective enzymes or transport proteins, resulting in a block of metabolic pathway. The male to female ratio is 1:1 for X-linked dominant if transmission is from mother to child (1). Effects are due to toxic accumulations of the substrates before block, intermediates from alternative metabolic pathways, defects in energy production and use caused by a deficiency of products beyond the block or a combination of these metabolic deviations. Figure I shows the theoretical consequences of metabolic disorders. Nearly every metabolic disease has several forms that vary in age of onset, clinical severity and often mode of inheritance. Proper history from parents has a role in suspecting IEM. Parental consanguinity increases the chance of autosomal recessive IEM (2).

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For evaluating an IEM the following five important aspects should follow:

1. History/ Family History – We should note whether the neonate was born to a consanguineous parents or not and also check previous history of older sibling like fetal deaths or miscarriages or genetically affected siblings and also note the pedigree for about two generations.
2. Physical examination like dermatitis, alopecia, facial dysmorphia, cataract etc.
3. Initial screening tests includes Complete blood count, Electrolytes level, Glucose, Ammonia, Lactate, Lactate/ Pyruvate ratio, Reducing substances, organic acids, Amino acids, Ketones.
4. Advanced screening tests: The test is performed on the basis of clinical context which includes long chain fatty acids, MPS separation and speciation, quantitation of amino acids, organic acids, carbohydrate and other metabolites.

5. Definitive diagnostic tests: To confirm the disorder detected, a specific enzyme assays in leucocytes, plasma/serum or red cells, immunoassays and DNA/ Mutation based analysis will be tested.

The diagnosis of metabolic disorders is challenging because of : 1. The episodic nature of metabolic illness. 2. The wide range of clinical symptoms that is also associated with more common conditions. 3. The low incidence of these disorders. 4. The consequent lack of experience among the pediatric sub-specialties and 5. The need for specialty testing (3).

Individual IEM are rare disorders, most having an incidence of less than 1 per 100,000 births. However, when considered collectively, the incidence may approach 1 in 800 to 2500 births. In one review of cases of IEM diagnosed in British Columbia (a predominantly Caucasian population) between 1969 and 1996, estimates of incidence of various classes of disorders were as follows (4):

- Amino acid disorders (excluding Phenylketonuria) — 7.6 per 100,000
- Phenylketonuria — 7.5 per 100,000
- Organic acidemias — 3.7 per 100,000
- Urea cycle diseases — 1.9 per 100,000
- Glycogen storage diseases — 2.3 per 100,000
- Lysosomal storage diseases — 7.6 per 100,000
- Peroxisomal disorders — 3.5 per 100,000
- Mitochondrial diseases — 3.2 per 100,000

In another review of cases of IEM diagnosed in the West Midlands of the United Kingdom (where approximately 11 percent of the population is from black and ethnic minority groups), the frequency of selected IEM during 1999 to 2003 were as follows (5):

- Amino acid disorders (excluding phenylketonuria) — 18.7 per 100,000
- Phenylketonuria — 8.1 per 100,000
- Organic acidemias — 12.6 per 100,000
- Urea cycle diseases — 4.5 per 100,000
- Glycogen storage diseases — 6.8 per 100,000
- Lysosomal storage diseases — 19.3 per 100,000
- Peroxisomal disorders — 7.4 per 100,000
- Mitochondrial diseases — 20.3 per 100,000.

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 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 (6).

Clinical findings

Table I, II, & III shows the symptoms associated with IEM, physical anomalies associated with inborn errors of metabolism and clinical manifestations in neonates.

IEM can affect any organ system and usually affect multiple

Table I : Clinical Symptomatology of Inborn Errors of Metabolism in the Neonate or Infant (1, 7)

	Symptoms indicating possibility of an IEM		Symptoms indicating strong possibility of an IEM
1.	Infant becomes acutely ill after period of normal behavior and feeding this may occur within hours or weeks.	1.	Persistent or recurrent vomiting
		2.	Failure to thrive (failure to gain weight or weight loss)
		3.	Apnea or respiratory distress(tachypnea)
2.	Neonate or infant with seizures and/or hypotonia, especially if seizures are intractable.	4.	Jaundice or hepatomegaly
		5.	Lethargy
3.	Neonate or infant with an unusual odor.	6.	Coma(Particularly intermittent)
		7.	Unexplained hemorrhage
		8.	Family history of neonatal deaths or of similar illness, especially in siblings
		9.	Parental consanguinity
		10.	Sepsis(Particularly *E.coli*)

organ systems manifestations vary from those of acute life threatening disease to sub acute progressive degenerative disorders. Categories of IEM are as follows (8):

1. Disorders of protein metabolism (eg. Aminoacidopathies, Organic acidopathies, Urea cycle defects).
2. Disorder of carbohydrate metabolism (e.g Carbohydrate intolerance disorders, Glycogen Storage Disorders, Disorders of Gluconeogenesis and Glycogenolysis)
3. Lysosomal storage disorders (e.g. Gaucher's disease, Niemann-Pick disease)
4. Disorder of Lipid metabolism (e.g. Fatty acid Oxidation Defects [Medium Chain Acyl Dehydrogenease Deficiency], Sphingolipidoses)
5. Mitochondrial disorders (e.g. Kearns-Sayre syndrome)
6. Peroxisomal disorders (e.g. Zellweger syndrome, Adrenoleucodystrophy).
7. Trace metal disorders (Menke's Kinky Hair syndrome, Wilson's disease).

Table II : Physical anomalies associated with acute onset inborn errors of metabolism (1, 7)

Anomaly	Possible IEM
Ambiguous genitalia	Congenital adrenal hyperplasia
Hair and/or Skin problems (alopecia, dermatitis	Multiple carboxylase deficiency, biotinidase deficiency, arginosuccinic aciduria
Structural brain abnormalities (agenesis of corpus callosum, cortical cysts)	Pyruvate dehydrogenase deficiency
Macrocephaly	Glutaric aciduria, type I
Renal cysts, facial dysmorphia	Glutaric aciduria, type II; Zellweger syndrome
Facial dysmorphia	Peroxisomal disorders, (Zellweger syndrome)
Cataract	Galactosemia, Lowe syndrome
Retinopathy	Peroxisomal disorders
Lens dislocation, seizures	Sulfite oxidase deficiency, Molybdenum cofactor deficiency.
Facial dysmorphia, congenital heart disease, vertebral anomalies.	3-OH-isobutyric CoA deacylase deficiency

Table III: Clinical manifestations of IEM presenting Neonatal (13)

Clinical manifestations	Symptoms
Neurologic signs	Poor suck, Lethargy (Progressing to coma), Abnormalities to tone, Loss of reflexes, Seizures.
Gastrointestinal Signs	Poor feeding, Vomiting, Diarrhea
Respiratory Signs	Hyperpnea, Respiratory failure
Organomegaly	Liver, Heart

A detailed classification is beyond the purview of this review. Hence only few examples are mentioned.

Common considerations in determining whether to screen for disorders are:

1. A disease that can be missed clinically at birth.
2. A high enough frequency in the population.
3. A delay in diagnosis will induce irreversible damages to the baby.
4. A simple and reasonably reliable test exists.
5. A treatment or intervention that makes a difference if the disease is detected early (8).

Screening is a basic tool for clinically suspected cases of inborn metabolic disease by a simple economical and effective technique like paper chromatography, TLC and some biochemical tests. However, it is not reasonable to make firm decision on the basis of screening test. HPLC is an acceptable technique to analyze and quantification of amino acids, organic acids and metabolites from biological fluids. Tandem Mass Spectrometry (TMS), GC/MS are the advanced technique for diagnosing metabolic disorders for confirmation. The Acylcarnitines in blood reflect the primary accumulating mitochondrial acyl-CoA metabolites in disorders of fatty acid and amino acid catabolism. Thus a acylcarnitine "profile" will recognize almost all of the defects in these pathways using the advanced technique like TMS (3). Advanced chemical diagnosis using GC/MS has also become an important part of the routine service. About 115 inherited organic and aminoacid disorders are diagnosed by employing a combination of GC/MS and an aminoacid analyzer and more than 910 cases and 80 inherited aminoacid metabolic diseases have been successfully identified since 1978. Among them lactic acidosis was the most frequently found inborn organic metabolic error comprising approximately 40% of total disorder (9).

The study report indicates the collective incidence of IEMs detected using qualitative and quantitative assays and consequently confirmed by confirmation test wherever possible. This study emphasizes the importance to diagnosis for IEM that helps early intervention in affected neonates.

Table IV: Classification of IEM based on size of molecule (13)

Small molecule	Large molecule
• Disorders of intermediary metabolism • Aminoacidopathies, Urea cycle defect, Organic acidemias, Fatty acid oxidation defect	• Storage disorders (Mucopolysaccaridoses, Glycogen storage disorders) • Accumulation of Protein, Carbohydrate, Lipids etc

STUDY REPORTS

We retrospectively reviewed eight hundred and sixty nine cases for age groups 40.2% <1 year, 19.9% 1-3 years, 13.5% 3-5 years, 18.4% >5Year and 8.0% adults were received in duration of two year with presenting symptoms of IEMs. 4 cc EDTA blood and urine of about 10cc were collected and when necessary C.S.F samples were also collected and stored at 4-8°C till the respective assay was performed the same day or the next day.

The important clinical findings as indicated by referrals of the eight hundred and sixty nine cases has 4.3% poor feeding, 6.4% lethargy, 4% failure to thrive, 10.6% seizures, 6% delayed milestones, 1.7% behavior disturbances, 2.8% irritability, 0.6% ataxia, 2.8% abnormal muscle tone, 0.92% attention deficit, 1.07% coma, 1.53% hepatomegaly, 0.61% splenomegaly, 7.2 % metabolic acidosis, 2% apnea, 0.92% skeletal abnormalities, 1.4% microcephaly, 2.2 % dysmorphic facial features, 4.4% hyopglycemia and 2.3% hyperammonemia. In 6.9% of the total cases (as indicated by referring clinician) consanguinity was noted.

The initial evaluation comprised of a complete blood count (CBC), measurement of serum levels of lactic acid, electrolytes, glucose, liver and kidney functions and plasma ammonia. Renal function was assessed by measurement of BUN and Creatinine. Hepatic functions were assessed by determinations of bilirubin, transaminases and Prothrombin time (8). All clinical data pertinent to the index case including current treatment regimen were collected. For samples referred from outside above mentioned data was sought. Cases where such data was not available are not considered in this review. Wherever a consanguinity or family history was evident, relevant details were noted.

All samples were subjected to a metabolic screening profile, the panel comprising of estimations of carbohydrates, amino acids, mucopolysaccharides, porphyrinuria, bile salts and pigments and organic acid metabolites. Techniques applied were High Performance Liquid Chromatography (HPLC), Gas Chromatography-Mass Spectrophotometry (GC-MS), Partition chromatography and fully automated cellulose acetate electrophoresis. Tandem Mass Spectrometry (TMS) was used for carnitine & Acyl Carnitines analysis.

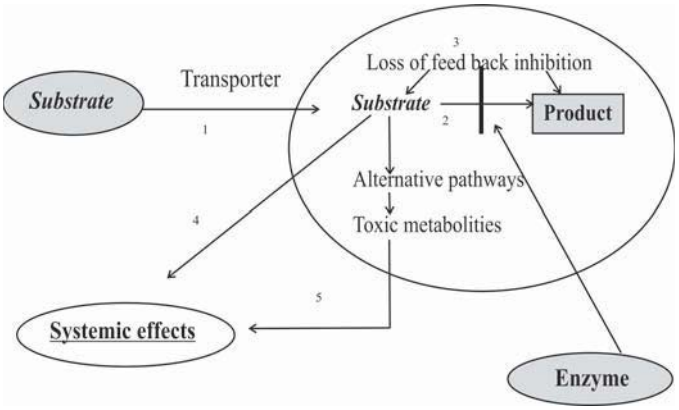
The enzyme assays were performed with leukocytes and erythrocytes when a specific enzyme was needed for confirmation. This assisted confirmation of diagnosis and decision on further treatment and management of the case.

Table V & VI shows the disorders detected in our laboratory (with no classification based on the class of disorder or metabolites) and the presenting symptoms of the respective cases. The youngest patient with a diagnosis from our data was 3 days old and the oldest was 49 years old. According to the data for disorders detected the male to female ratio is 15:11, whose significance is to be determined.

CONCLUSION

Inborn errors of metabolism causing clinical manifestations in the neonatal period are usually severe and are often lethal if proper therapy is not promptly initiated. Clinical findings are

Fig I: Diagrammatic representation of causes and consequences of metabolic disorders



1. Substrate is transported into a cell with the help of transporter, deficiency of transporter leads to IEM. 2. Substrate is converted to product in the presence of catalyst, if the enzyme is deficient which leads to IEM. 3. The substrate is converted to product, the accumulation of product obtains in case of loss of feed back inhibition leads to metabolic disorders. 4. Due to metabolic defects, substrate is not converted to product and accumulation of substrate leads to systemic effects. 5. If substrate is not converted to product due to enzyme or cofactor deficiency, it enters to alternative pathway and produce toxic metabolites which lead to systemic effects in turn causes presenting features of inborn errors of metabolism.

Table V: Metabolic defect or disorders diagnosed in our laboratory

Age/ sex	Disease/ Disorder	Methodology	Defective metabolite	Results			Treatment / follow-up suggested
				Specimen	Values	Reference range	
3d/M	Nonketotic Hyperglycinemia	HPLC aminoacids	Glycine	Plasma C.S.F*	1034 μmol/l 113.74 μmol/l	100-500 μmol/l 5-10μmol/l	Child expired.
18m/M	Fanconi-Bickel syndrome	Partition chromatography	Aminoacids, carbohydrates	Urine	Generalized Glucosuria and	aminoaciduria, Galactosuria	Child was discharged with advice on diet.
25d/F	Maple Syrup urine disease (MSUD)	HPLC aminoacids	Leucine	Urine	241.7 μmol/ g creatinine	19-177μmol/ g creatinine	MSUD diet suggested. Child is now doing well.
4 m/M	3-Hydroxy-3-Methylglutaric aciduria	TMS	#C6DC	Urine	0.46 μmol/l	0.25 μmol/l	Child was discharged with restriction in diet and is now doing well.
10Y/F	Aspartyl glucosaminuria	GC-MS¥	Aspartyl glucosamine				No known treatment but child is on a planned diet and still under observation.
11d/M, 5Y/F, 3m/M, 26d/M, 16Y/M, 2Y/F, 4Y/F	7 cases of Primary Carnitine deficiency	TMS	Carnitine	Dried Blood spot	20 μmol/l 16.5 μmol/l 5 μmol/l 10 μmol/l 2.0 μmol/l 2.0 μmol/l 0.5 μmol/l	24.7-66.6 μmol/l	Carnitine supplementation.
22d/F	Tyrosinemia Type I	HPLC aminoacids	Tyrosine	Plasma	325μmol/l	30-100 μmol/l	Detected at end stage. Child expired.
13Y/M	Type II b-Hyperlipoprot-einemia	Cellulose acetate Electrophoresis	Increased VLDL^{+} and decreased HDL$^{¤}$. No Chylomicron.	Plasma	HDL$^{¤}$-5.1% VLDL^{+}-40.5% Chylomicron -0%	HDL$^{¤}$-25-40% VLDL^{+} - 10-36% Chylomicron - 0-2%	Surgical corrections of CAD^{ä} followed by dietary advise.
3m/ F	Type III-Hyperlipoprot-einemia	Cellulose acetate Electrophoresis	Increased Chylomicron and VLDL^{+} moderately decreased HDL$^{¤}$. No LDL	Plasma	Chlylomicron-21.2%, VLDL^{+}-56.4%, HDL$^{¤}$-22.4%, LDLy-0%	Chylomicron-0-2%, VLDL^{+} - 10-36 %, HDL$^{¤}$-23-54%	Lost for follow up
27 Y/ M	Ornithine aminotransferase deficiency	HPLC aminoacids	Ornithine & Lysine	Plasma Plasma	Ornithine-908μmol/L Lysine-28.09 μmol/L	20-200 μmol/L 40-300 μmol/L	Arginine restricted diet, Pyridoxine supplementation, Periodic monitoring of aminoacid levels.
3d/M, 2Y/M.	2 cases of Dilated Cardiomyopathy with Propionic acidemia	HPLC organic acids	Propionic acid	Urine	5.90 mmol/ mmol creatinine 4.59 mmol/ mmol Creatinine	0.1-1.7 mmol/ mmol creatinine	Protein restriction, Biotin supplementation
8Y/M	Pompe's disease (GSD II)	Enzyme assay in leukocytes	Activity of α-glucosidase	Leukocytes	Negligible	0.32-0.5 μmol/ g protein /min	Under cardiologist.
11d/M, 4m/F	2 cases of Methylmalonic Acidemia	TMS	C3 Acyl Carnitine	Dried blood spot	13.05 μmol/l	3.50μmol/l	Detected at end stage. Child treated with B_{12}, Carnitine and Biotin. Child expired

Age/ sex	Disease/ Disorder	Methodology	Defective metabolite	Results			Treatment / follow-up suggested
				Specimen	Values	Reference range	
9Y/F	Biotin - dependent state	HPLC organic acids	Biotin metabolism	Urine	1.01 mmol/ mmol Creatinine	0.1-1.7 mmol/ mmol Creatinine	Confirmed by enzyme assay. On Biotin supplementation, regular follow- up.
3Y/F	Sandhoff's disease	Spectrofluro-photometry	Sphingolipid metabolic defect	Plasma	12.10%	30-40%	Confirmation of Mutation. Referred to Clinical Geneticist
10m/F	Tay-Sachs disease	Spectrofluro-photometry	Ganglioside metabolic defect	Plasma	3.43%	50-60%	Being followed at referral hospital
6m/M	Beta Ketothiolase deficiency	TMS & Urine GC/MS	Isoleucine metabolism	Dried blood spot & Urine	C4 – 1.23 C5-OH-3.935 C5:1- 1.635 C5:1/C2-1.65 Elevated 3-hydroxy butyrate, Acetoacetate, 2-methyl-3-hydroxy butyrate, Methylacet-oacetate, Tiglylglycine.	C4 – 0.90 C5-OH-0.40 C5:1- 0.20 C5:1/C2-0.20	Protein restricted diet, regular follow up.
49Y/M	α-Galactosidase	Enzyme assay in leukocytes	Glycolipid metabolism	Leukocytes	5.79 nmol/hr/ mg	32.9 nmol/hr/mg	Being followed at referral hospital

C.S.F*-Cerebrospinal Fluid, C6DC$^{\#}$- Six carbon Dicarboxylic acid, GC-MS$^{¥}$ - Gas chromatography-Mass Spectrometry, VLDL^{+}-Very low density Lipoprotein, HDL$^{¤}$- High Density Lipoprotein, ^{ä}CAD-Coronary Artery Disease, LDLy- Low Density Lipoprotein.

usually non-specific and similar to those seen in infants with sepsis. An inborn error of metabolism should be considered in the differential diagnosis of a severely ill neonatal infant, and special studies should be undertaken if the index of suspicion is high. It has been shown that if detected early complication in these disorders could be easily prevented with dietary restriction of the offending food constituent of metabolite (10).

All the eight hundred and sixty nine that were considered for the study were first subjected to screening for a possible IEM. Among them about 2.65% of the cases indicated the presence of IEM. The positive cases were confirmed by performing the relevant confirmatory tests. Even though IEM are rare, the results emphasize that they are collectively common. Most of the metabolic disorders can be detected in the neonatal period. For Tyrosinemia type I, urinary succinyl acetone was not standardized in our lab at the stage, when the samples had arrived. Depending on the clinical symptoms, clinician inputs and high tyrosine level, the case was presumptively recorded as a Tyrosinemia Type I. Detecting a disorder much earlier means early initiation of treatment and possibly retards the progression of the disorder. Some of these disorders tend to become difficult to manage when detected too late and some could be fatal too. Adding to the burden is the lack of adequate awareness about these disorders and the existing treatment modalities among the clinical fraternity and misconceptions about them in the general population (11).

With investigation like TMS and GC-MS available today, a diagnostic revolution may not be far away. The TMS alone can detect 35-40 metabolic disorders and has revolutionized the concept of newborn screening in the developed countries. This may be difficult for developing countries to follow given the socio-economic considerations. HPLC and GC-MS for IEM are probably to be adapted in developing countries for reasons of affordability without compromise on the quality. The high numbers of screen positives observed in the screening panel of tests is of fundamental importance for directing the clinical investigation. It depends on an intimate association between the interpretations of the biochemical and metabolic tests and a specialized multidisciplinary clinical investigation. Inborn

Table VI: Presenting symptoms and defective enzyme/ metabolic defect of the disorders (indicated in Table V) detected at our center per clinician notes.

Disease/ Disorder	Defective Enzyme/ Metabolic defect	Presenting symptoms
Nonketotic Hyperglycinemia	Glycine cleavage system	Hypoglycemia, hypotonia, coma, poor feeding, lethargy, hyperammonemia.
Fanconi-Bickel syndrome	Reabsorption defect	Hepatomegaly, nephromegaly, dyslipidemia, rickets, glucose and Galactose intolerance.
Maple Syrup urine disease	α-Ketoacid decarboxylase	Body fluid odor that resembles maple syrup, vomiting, lethargy, seizures, coma.
3-Hydroxy-3-Methylglutaric aciduria	HMG CoA Lyase	Vomiting, dehydration, hypoglycemia, metabolic acidosis, lethargy, coma, convulsions, delayed milestones.
Aspartyl glucosaminuria	Aspartyl glucosaminidase	Progressive psychomotor retardation, coarse facial features and mild osseous abnormalities.
Primary Carnitine deficiency	Carnitine uptake	Encephalopathy, hepatomegaly, skeletal myopathy, apnea, hyperammonemia, developmental delay, nonspecific abnormal problems, Hypoglycemia and Cardiomyopathy.
Tyrosinemia Type I	Fumaryl acetoacetate hydroxylase	Liver cirrhosis, peripheral neuropathy, renal tubular disorders, polyneuropathy, episodes of intense abdominal pain.
Type II b Hyperlipoproteinemia	Abnormal presence of lipids and lipoproteins.	Elevated plasma cholesterol or triglyceride levels, Xanthoma, CAD.
Type I Hyperlipoproteinemia	Slow clearing of Chylomicrons.	Elevated plasma triglyceride levels, eruptive xanthomas and recurrent abdominal pain.
Ornithine aminotransferase deficiency	Ornithine aminotransferase deficiency	Gyrate atrophy, Chorio-retinal degeneration and Progressing decreasing vision.
Dilated Cardiomyopathy with Propionic acidemia	Propionyl carboxylase deficiency	Dilated Cardiomyopathy.
Pompe's disease	Lysosomal glucosidase	Massive Cardiomyopathy, Muscle hypotonia, Progressive dysfunction of skeletal muscle.
Methylmalonic Acidemia	Methylmalonyl CoA isomerase	Poor appetite, Vomiting, Extreme sleepiness, floppy muscle tone, Seizures, Stroke, metabolic acidosis.
Biotin dependent state	Holocarboxylase Synthase	Mild MR, Myoclonic jerks, delayed milestones, Alopecia, Biotinidase-normal activity.
Sandhoff's disease	Hexosaminidase B	Hepatosplenomegaly with cardiac disease.
Tay-Sachs disease	Hexosaminidase B	Developmental delay, B/L Cherry red spot, Myoclonic jerks, Startle response
Beta ketothiolase deficiency	Beta ketothiolase	Dehydration, difficulty in breathing, Lethargy, Occasional seizures and Ketoacidosis.
Fabrys disease	α-Galactosidase	Episodes of pain, particularly in the hands and feet, clusters of small, dark red spots on the skin called angiokeratomas, cloudiness of the front part of the eye (corneal opacity).

errors of metabolism must be suspected whenever a patient presents metabolic disturbances or neurological manifestations without a determined cause. Always correlate the metabolic screen results with the clinical picture because, if the patient has liver disease and tubular defects aminoaciduria will be present and if it is hypo perfusion, also show lactic acidemia. Some of the drugs may also interfere with the analysis for eg. Valporate intake leads to ketone positive on the urine dipstick tests and Topiramate, Acetazolamide might produce lactic acidemia. A single negative test should not be used to exclude IEM in all cases. The time of testing, particularly in episodic disorders, stress testing following well defined protocol, clinical picture and details of drugs taken should be considered for arriving at a final diagnosis. Lack of indigenous External Quality Assurance programs is a cause of worry (12).

IEM are typically genetic disorders, family members need to be counseled about the probability of the next offspring being affected. It is of utmost importance to families who have a known history of such occurrences (13). Genetic counseling is assuming significance in India too (14). The diagnosis of an inborn error of metabolism often needs to be established quickly in order to prevent death or permanent neurological sequelae.

An IEM could be a diagnosis of inclusion rather than exclusion. For the small number of babies who may have one of these disorders, appropriate and timely care can make a lifetime of a difference!

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