

## Inborn Error of Metabolism –An Indian Perspective

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**KEYWORDS** Inborn error of metabolism; genetic; inherited metabolic disorder; neurology

**ABSTRACT** Inborn errors of metabolism (IEM) constitute a diverse heterogeneous group of disorders with protean clinical manifestation presenting mainly in the pediatric population. Though individually rare, together they constitute a significant percentage of children seen in genetic and neurology clinics. With the recent advancement of knowledge of genetic engineering and awareness of clinical presentation of IEM, early diagnosis and treatment facilities has dramatically changed the whole perspective of morbidity and mortality of infants (Burton 1998). This review focuses on selected IEMs and highlights those seen in the neonatal period. Data from Indian centers are presented. It also emphasizes principles of management in these difficult disorders in the context of developing country (Kumta 2005).

### INTRODUCTION

There is an accelerating demographic switch from communicable diseases to genetic disorders. The expression of genetic disease is the combined effect of genes and the environment. There are 25 million births India annually; 8 lakhs are born with congenital malformation; 3.5 lakhs with glucose 6 phosphate deficiency (G6PD); 25,000 with metabolic disorders; 20,000 with Down Syndrome, 15,000 with congenital hypothyroidism, 14,000 with thalassaemia and 5,000 with sickle cell anemia. In India biochemical screening of 4400 cases of mental retardation revealed that 5.75% (256 cases) were due to various inherited metabolic disorders (ICMR 1991; Verma 2000). 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. IEMs are individually rare but are collectively common. 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 of clinical presentation varies from child to child and the form of presentation is also variable according to age. Environmental factors may trigger the onset and severity of disease. It also depends upon the degree of accumulation of toxic substances before the metabolic block e.g. diet, intercurrent, infections, fasting, drugs etc.

### MECHANISM OF METABOLIC DISORDERS

EAB is an enzyme converting 'A' into 'B'.

EBC, the enzyme converting 'B' into 'C', is absent and is the cause of the IEM. This leads to accumulation of substrate 'B' to abnormal level which then gets diverted to an abnormal metabolic pathway to yield a toxic metabolite 'D'. 'B' or 'D' could be toxic. 'B' and 'D' could be detected and 'EAB' can be estimated biochemically.

**Importance of History:** Proper history from parents has an important role in suspecting IEMs. Parental consanguinity increases the chance of autosomal recessive IEMs. History of 'sudden infant death' (SID) or 'unexplained neonatal death' (UND) in sibs or maternal male relatives is a clue to IEM. History of dietary intake e.g., cane sugar in Hereditary Fructose Intolerance or milk in Galactosaemia, is also important for clinical suspicion. Regression of milestones or developmental delay are positive clinical history in differential diagnosis of IEM.

**Neonatal IEMs:** If a term male baby delivered normally following uncomplicated pregnancy is apparently well but suddenly deteriorates – one should always consider IEM. Or without any risk or source of sepsis if a new born suddenly develops symptoms of sepsis – IEM must be excluded along with septic work up. So for any critically ill neonate – IEM should always be excluded. Early diagnosis of neonatal IEM is crucial for three reasons.

1. The condition is rapidly progressive and causes irreversible damage.

2. The treatment can often be effective if commenced early.

3. Correct early diagnosis helps in genetic counseling.

**Clinical finding of Neonatal IEMs:** Usually new born baby is normal for the first three or four days of life, after which this disorders presents due to intake of dietary proteins carbohydrates etc. Though individual disorder may be uncommon, they are fairly common when considered together. IEMs are usually recessive disorders but often affect only one sib (Scriver et al. 1995). IEM has a characteristic inheritance pattern e.g. Fabry's disease, Menkes disease and Hunters disease are X-linked recessive and most other are autosomal recessive. The predominant symptoms and signs are poor feeding, feeding intolerance, failure to thrive, seizure, vomiting, temperature instability, tachypnoea, apnea, irritability, abnormal movements etc. (all the above are features of septicaemia). Emergency adequate laboratory facilities to diagnose neonatal IEM are scarce and lacking in India leading to delay in diagnosis, treatment and hence a poor prognosis in most cases.

**Specific Features of Neonatal IEMs:** Abnormal urine or body odor is characteristic of some IEM, Maple Syrup Urine Disease – maple syrup or burnt sugar smell. Isovaleric acidaemia – sweaty feet smell. Phenylketonuria – mousy smell. Tyrosinaemia – rancid or fishy odor .

Diarrhoea–severe watery–Galactosaemia, Primary sucrase, lactase, isomaltase deficiency, chloric diarrhoea – Bile acid disorder, Infantile Refsum disease. Dolmans disease.

Cardiomyopathy/cardiac failure–Pompe's disease, (Glycogen storage disease GSD–II). Fatty acid oxidation (FAO) defects.

Hepatomegaly – Galactosaemia, Tyrosinemia, Alfa 1 antitripsin deficiency.

Hepato splenomegaly–Gaucher's disease, Niemann-pick type A .

Seizures – Pyridoxine deficiency or dependency, Nonketotic hyperglycinemia.

**Clinical Findings (1 months – 5 years):** When IEMs are of moderate severity, they generally present either in infancy or early childhood (Emery and Rimoin1996) with poor feeding, failure to thrive, dysmorphic or coarse features, abnormalities of hair or skin, The children may develop symptoms rapidly and takes longer period to recover than normal children. There may be recurrent episodes of vomiting, ataxia, seizures, lethargy and coma or fulminant hepatoencephalopathy (like Reye Syndrome), Delay in milestones of development, with occasional regression of milestones, Ataxia,

hypo-or hypertonia, auditory and visual disturbances due to: Cataracts in Galactosaemia, Lowe syndrome, Zellweger syndrome, Dislocation of lenses–in Homocystinuria, Retinal degeneration in Peroxisomal disorder, Corneal clouding and congenital glaucoma (K-F ring) occurs in (Wilson's disease).

**In Older Children, Adolescents and Adults:** These IEMs are of very mild variety or there may be partial absence of specific enzymes. Common findings are mild to gross mental retardation, autism, behavioral disturbances, learning disorders, delirium, agitation, rage, panic attacks, seizure, ataxia, muscle weakness, paraparesis, Adolescent females with history of protein aversion, abdominal pain and migrane-like headaches are found to have lysosomal storage disorders (Lyon et al. 1996)

## INVESTIGATIONS

**Neonatal Screening:** for Hypothyroidism, Phenylketonuria, Galactosaemia, Congenital Adrenal Hyperplasia, Homocystinuria, Maple Syrup Urine Disease are commonly carried out.

**Initial Laboratory Evaluation:** CBC (Complete Blood Count)–to screen anaemia, neutropenia, thrombocytopenia, blood urea nitrogen and creatinine – for renal status and liver function tests are also carried out.

Other test are prothrombin and activated partial thromboplastin time for hepatic status, Serum electrolytes, bicarbonate, blood gases, **Ammonia:** in children with altered level of consciousness, persistent recurrent vomiting, primary metabolic acidosis, Preferable arterial blood, Normal values – Neonates = < 100 mg/dl, Infants = < 80 mg/dl blood glucose and urine for ketones and reducing substances. **Enzyme assay or DNA analysis:** from WBC, RBC, Liver, Skin fibroblasts lead to the final diagnosis

## BASIC PRINCIPLES OF TREATMENT

Restriction or elimination of potentially harmful proteins or sugars from diet to prevent accumulation of toxic levels of the precursor substances. In majority of aminoacid disorders – human breast milk is relatively safe, except galactosaemia, as its protein load is least (1 mg %). Animal milk is unsafe because of its high lactose content (Fishler et al. 1980).

Supply of deficient product, electrolytes Vitamins and agents to detoxify and acceleration

of excretion of toxic metabolites like carnitine in life-threatening conditions in primary metabolic acidosis or hyperammonaemia. Sodium Phenyl acetate and Sodium Benzoate—to reduce ammonia. Arginine—in some urea cycle defects.

In severe hyperammonaemia and resistant life threatening metabolic acidosis: haemodialysis with Ammonia > 500-600 micro gram /dl used Peritoneal dialysis has < 10% efficacy than haemodialysis haemodialysis is not available, Double volume exchange transfusion – even less effective.

For a critically ill child (ABC) of resuscitation should be initiated

- A = Maintenance of airway,
- B = Maintenance of breathing,
- C = Maintenance of circulation.

### CONCLUSIONS

IEMs are “Single gene defects” individually rare, but collectively common. A high index of suspicion is most important in making the diagnosis: Always to consider IEM in any critically ill neonate. If a child becomes severely symptomatic in a routine infection and takes unusually longer time to respond to treatment – always should exclude IEM. One should have a knowledge of broad clinical manifestations of IEM which will provide the clue to diagnosis. Adequate laboratory facilities are essential for emergency diagnosis, recent advances in diagnosis and treatment have significantly improved the prognosis of infants with IEM. But unfortunately in India – these facilities are scarce

and lacking, leading to delay in diagnosis and treatment – resulting in poor prognosis (Murjan 2004). Early clinical and laboratory diagnosis along with adequate treatment can provide these children a meaningful normal life. In children with IEM cerebral palsy (CP) is preventable.

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