Screening for Inborn Errors of Metabolism in Critically ill Newborn

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Objective: Newborn screening for Inborn Errors of Metabolism is not a routine practice in India. There have been isolated reports on IEM in Indian children, however there is no data available on relative or true incidence of IEM in critically ill newborns. We sought to determine the incidence of various genetic and metabolic disorders in critically ill newborns in NICU setup and to determine the feasibility of comprehensive newborn screening for early identification of these disorders.

Methods: Total 286 critically ill newborns admitted over last 4.5 years in NICUs were studied in detail for genetic and metabolic disorders. We used basic metabolic workup – including ammonia, lactate, blood sugar level, serum electrolytes, venous blood gases, uric acid, CBC along with 2nd level investigations like urine metabolic screening tests, thin layer chromatography for amino acids, sugars and organic acids, GALT enzyme and Biotinidase enzyme assay. Of these 286 children, 201 babies were also subject to urine GC/MS and Acyl carnitine profile by tandem mass spectrometry. Additional investigations of leukocyte enzyme assay and/or Karyotype were asked for in babies with organomegaly or dysmorphic features.

Physical Examination (1): Usually the physical examination is not very contributory to the clinical assessment in CINB. However the clinical findings which are important from the point of view of IEM are listed below. We always attempt to record these in every baby referred to rule out IEM.

1. Facial dysmorphism
2. Coarse facies
3. Cataracts and retinopathies
4. Typical brittle/sparse/light colored hair
5. Hepatospleenomegaly
6. Genitalia (ambiguous/ normal)
7. Structural brain abnormalities (megalo/ microcephaly)
8. Hypertrophic / dilated cardiomyopathy
9. Myopathy (floppy baby)
10. Specific odor of urine

Basic Lab Investigation (1): We perform following investigations on all the critically ill newborns.

1. CBC/ Band cell count
2. Sr. Electrolytes and ABG
3. Calculate Anion Gap
4. Blood Glucose levels
5. Plasma Ammonia
6. Plasma Lactate
7. Plasma Pyruvate
8. Sr. Uric acid
9. G6PD
10. SOS- CSF Routine and Lactate

Specific Metabolic Investigations (1): Once a metabolic disorder is suspected, we undertake following detailed investigations to identify specific Inborn Errors of Metabolism. No single test is diagnostic of any IEM. A battery of advanced tests is required to come to a conclusion. As there are more than thousand known IEMs and the number is increasing every day, it is not reliable to perform only one test to identify IEM. We have to choose from ever expanding menu of tests available for CINB.

1. Urine Metabolic Screening tests (25 tests)
2. Thin Layer Chromatographies for amino acids, organic acids and sugars
3. GALT enzyme assay with Total Galactose
4. Biotinidase enzyme assay
5. 17 OHP and T4
6. HPLC amino acids (Plasma and CSF)
7. Urine GC/MS (Preferably quantitative)
8. Total and free Carnitine levels
9. Acyl Carnitine profile
10. Homocysteine levels
11. Total Cholesterol and 7 DHC by HPLC or GC/MS
12. VLCFA analysis ant other fatty acids
13. Iso electric focusing for Transferrin and TBG
14. Specific enzyme analysis
15. DNA mutation studies

Results: Of 286 babies registered for IEM workup, only 201 babies received detailed metabolic screening. 85 babies were labeled as incompletely investigated. The reasons for incomplete investigation were 1. Parents refused further investigation or 2. Babies were transferred to other NICUs for further care. Of these 201 babies with detailed metabolic workup 19 babies did not have any IEM and were septicemia (12), TORCH infections (4), extended physiological jaundice (1), Hypoxemic Ischemic Encephalopathy (2). Of 182 babies with genetic and metabolic defects 124 babies had IEM. The commonest IEM detected in our patients were Galactosemia (18), Biotinidase def. (8), partial Biotinidase def. (24), MSUD (8), Tyrosinemia (1), Homocysteinuria (1), CAH (4), Hypothyroidism (1), Propionic acidemia (4), Methylmalonic acidemia (2), Isovaleric acidemia (2), Fructose 1,6 diphosphatase def. (1), Ketothiolase def. (1), CPT1 def. (1), CPT2 def. (4), MCAD def. (1), LCHAD def. (1), severe carnitine def. (1), HMG CoA Lyase def. (1), Respiratory chain defects (8), GA type 2 (5), Cystic fibrosis (3), G6PD def. (2).

Management (4): It is difficult to provide all the details of management aspect in one single poster. Readers should consult the specific references provided below. Steps in management-

Step I: High supply of glucose
Step II: Adaptation of therapy according to the results of the basic laboratory investigations
Step III: Specific therapy derived from the results of specific metabolic investigations (details are provided in table)
Step IV: Precautions before discharging the patient from hospital
Step V: Genetic counselling

Drug	**Disorder**	**Dosage** (given in 3 doses if not indicated differently)
Arginine HCl (10%)	Urea cycle defect (except for Arginase def.)	0. 20 – 0.60 gm/kg/day – IV
Betaine	Disorders of Homocysteine metabolism	250 mg/kg/day - PO
Biotin	1. Holo carboxylase synthase def. 2. Biotinidase def. 3. Hyperlactic acidemia	10 – 15 mg/day – PO
L- Carnitine	1. Organic aciduria 2. Carnitine transporter defect 3. FAOD	50 – 300 mg/kg/day – IV / PO

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	4. Mitochondrial disorders	
Citrulline	1. CPS and OTC def. 2. NAGS def	170 mg/kg/day
Diazoxide	Hyperinsulinism	15 mg/kg/day - PO
Folic acid	Disorders of Homocysteine metabolism	15 mg/kg/day – IV / PO
Folinic acid	Folinic acid responsive disorders	3 – 5 mg/kg/day – IV
Glucagon	Hyper insulinism	Bolus 30 – 100 ug/kg (max 1mg.)
Hydroxy cobalamin	1. Methylmalonic aciduria 2. Disorders of homocysteine metabolism	500 – 1000 ug IM / IV
Insulin	Neonatal Diabetes Mellitus	0.05 – 0.10 U/kg/hr – IV drip
Methionine	Disorders of re-methylation	100 mg/kg/day – PO
NTBC	Tyrosinemia type 1	1 – 2 mg/kg/day – PO
Pyridoxine	1. Pyridoxine responsive seizures 2. Hyper homocysteinemia	100 – 500 mg/day – IV / PO
Riboflavin	1. Glutaric aciduria type I & II 2. Hyperlactic acidemia	150 mg/day - IV / PO
Sodium Benzoate	1. Hyper ammonemia 2. Urea cycle defect 3. NKHG	100 – 500 mg/kg/day – PO
Sodium phenylbutyrate	1. Hyper ammonemia 2. Urea cycle defect.	250 mg/kg/day
Thiamine	Hyper lactic acidemia	150 mg/day - IV / PO

Conclusion: These results suggest that Inborn Errors of Metabolism are not rare as a whole group and we do see almost all types of IEMs in critically ill newborns. Comprehensive metabolic screening for 30+ disorders will detect almost 68.13% of all IEMs in these babies. We hereby strongly recommend comprehensive screening in any critically ill newborn at the time of admission in NICU.

References:

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