Research Article

Study of Clinical Profile of 5 Cases of Inborn Errors of Metabolism in Critically Ill Children - In Tertiary Care Teaching Hospital Attached to Bangalore Medical College and Research Institute - Bangalore, Karnataka (India)

Laxmi M and Nagesh*

Department of Paediatrics Bangalore Medical College and Research Institute, Bangalore, Karnataka, India

ARTICLE INFO

Received Date: May 01, 2018
Accepted Date: May 23, 2018
Published Date: March 18, 2019

KEYWORDS

Tandem mass spectroscopy
Inborn error of metabolism
New-born screening
Intensive care unit

Citation for this article: Laxmi M and Nagesh. Study of Clinical Profile of 5 Cases of Inborn Errors of Metabolism in Critically Ill Children - In Tertiary Care Teaching Hospital Attached to Bangalore Medical College and Research Institute - Bangalore, Karnataka (India). SL Clinical Medicine: Research. 2019; 2(1):114

Corresponding author:
Nagesh,
Department of Paediatrics Bangalore Medical College and Research Institute, Bangalore, Karnataka, India,
Email: drnagesh.m1983@gmail.com

ABSTRACT

Introduction: Inborn Errors of Metabolism (IEM) are heterogeneous group of disorders caused due to single gene defect which may manifest immediately after birth or within few days or weeks after birth. A large number of Inborn Errors of Metabolism (IEM) in children remain undetected in India due to lack of investigative facilities and economic restraints. Most of the IEM result from defects in any of the key enzymes of various metabolic pathways, leading to accumulation of compounds which follow an alternative pathway of metabolism, resulting in the production of toxic metabolites and deficiency of biologically important compounds. Those causing clinical manifestations in the neonatal period are usually severe and often lethal and may present with neurologic or metabolic disturbance like – poor feeding, lethargy, failure to thrive, seizures, apnea, drowsiness, coma and later on there may be gross delay in the development of milestones.

Objective: To study the clinical and laboratory profile and outcome of five patients with inborn errors of metabolism presenting to the Neonatal intensive care unit (NICU) and Paediatric intensive care unit (PICU) in a tertiary care teaching hospital, Bangalore Karnataka-India.

Methods: This is a Hospital based cross-sectional study carried out at Bangalore Medical College and Research Institute-Bangalore Karnataka India, between November 2015 to April 2017, in which the five children (cases) presenting with features suggestive of Inborn Errors of Metabolism attending a tertiary care Neonatal intensive care unit (NICU) and Pediatric Intensive care unit (PICU) were included in the study. The informed consent was taken from the parents (Guardian) of the child. All the five cases were subjected to screening tests and other relevant investigations. A detailed history regarding parental consanguinity and sibling deaths, birth history and postnatal development of the child was obtained from the parents in the predesigned proforma and recorded. A thorough clinical examination was also carried out in these children.

Results: Five Children with suspected features of Inborn Errors of Metabolism who were admitted in our Neonatal intensive care unit and Paediatric intensive care unit were noted and analysed. After taking thorough history from parents, clinical presentations, laboratory investigations, the diagnosis of these five cases of inborn errors of metabolism were made, analysed and interpreted. We have come across five interesting cases in the course of our study- (1) Propionic acidemia (2) Branched

chain aminoaciduria (3) Galactosemia (4) Glycogen storage disorder (5) Gaucher's disease. Among the five cases studied, the Branched chain aminoaciduria case was died, so mortality being 20 % and other 4 cases are on regular follow up visit. Clinical presentation was quite varied in all the five cases. Among five cases of IEM, two of them were female and three were male. All the five children were born to consanguineously married couples. NBS was positive for Galactosemia and history of elder sibling death at the age of 1 month was noted in the same case.

Conclusion: One of the cases in our study was presented with features suggestive of late onset sepsis, persistent vomiting, breathlessness, fever, convulsion and delayed motor milestone was diagnosed as Propionic acidemia. One more child was presented with features suggestive of late onset sepsis, refusal of feeds and lethargy, hurried breathing and chest in drawing with history of 1 abortion at 3 months in previous pregnancy, on proper investigation the child was diagnosed as Branched chain aminoaciduria. The other child was presented with excessive vomiting and persistent jaundice, NBS was positive for Galactosemia and history of elder sibling death at the age of 1 month having similar features was found to be Galactosemia after thorough work up. A female child was presented for the first time at the age of 3 years having distension of abdomen, Splenohepatomegaly for 2 years, was diagnosed to be Glycogen storage disorder after the liver biopsy was done. A 4-year 2 months old male child was presented for the first time with features of distention of abdomen, massive splenomegaly, Pneumonia and Pancytopenia was found to be suffering from Gaucher's disease when we had done bone marrow biopsy which showed typical features suggestive of Gaucher's disease.

INTRODUCTION

Inborn Errors of Metabolism (IEM) are heterogeneous group of disorders caused due to single gene defect which may manifest immediately after birth or within few days or weeks after birth [1]. Garrod first described 4 Inborn Errors of Metabolism in the first decade of last century. Now after 100 years, the number of Inborn Errors of Metabolisms has increased from 4 to 500 [2]. Individually, IEM present variable incidences but as a whole, they present a cumulative frequency of 1:500 newborns [3]. Strong suspicion of IEM can be done if the child presents with any of the following features – parental consanguinity, sibling deaths, positive family history of similar illness/deaths, convulsions, regression of milestones, mental retardation, ketosis, acidosis, persistent hypoglycemia, jaundice, organomegaly, dysmorphic features or coarse facial features, unusual odour to urine [4,5]. India has a population of more than 1.1 million people with almost 28 million annual births, there is also high rate of consanguinity and a high incidence of genetic disorders, we can expect 18,000-20,000 babies were being born every year with IEM in India [6-8]. The diagnosis of IEM in critically ill newborns require a Pediatrician or a neonatologist, experienced in diagnosis and management of IEMs along with a dedicated laboratory which performs these biochemical investigations frequently, standardizes and upgrades these tests on regular basis [9]. Unexplained death or sudden death may be due to an IEM which may be suspected if there is a history of previous sibling similarly affected and in consanguineously married couples [10].

MATERIALS AND METHODS

This is a Hospital based cross-sectional study carried out at Bangalore Medical College and Research Institute-Bangalore Karnataka India, between November 2015 to April 2017, in which the five children (cases) presenting with features suggestive of Inborn Errors of Metabolism attending a tertiary care Neonatal intensive care unit and Pediatric Intensive care unit were included in the study. The informed consent was taken from the parents (Guardian) of the child. All the five cases were subjected to screening tests like tandem mass spectrometry (TMS) when indicated, the samples were collected on filter papers, air-dried and then sent to laboratories for analysis and other relevant investigations were also sent. A detailed history regarding parental consanguinity and sibling deaths, birth history and postnatal development of the child was obtained from the parents in the predesigned proforma and recorded. A thorough clinical examination was also carried out in these children. Five Children with suspected features of IEM were noted and analysed. After the diagnosis of Inborn Error of Metabolism was made in them, were managed as per standard protocols of management of IEM which were available at our Pediatric intensive care set up.

RESULTS

Five Children with suspected features of Inborn Errors of Metabolism who were admitted in our Neonatal intensive care unit and Paediatric intensive care unit were noted and analysed. After taking thorough history from parents, clinical presentations, laboratory investigations, the diagnosis of these five cases of inborn errors of metabolism were made, analysed and interpreted. We have come across five interesting cases in the course of our study- (1) Propionic acidemia (2) Branched chain aminoaciduria (3) Galactosemia (4) Glycogen storage disorder (5) Gaucher's disease. Among the five cases studied, the Branched chain aminoaciduria case was died, so mortality being 20 % and other 4 cases are on regular follow up visit. Clinical presentation was quite varied in all the five cases. Among five cases of IEM, two of them were female and three were male. All the five children were born to consanguineously married couples. NBS was positive for Galactosemia and history of elder sibling death at the age of 1 month was noted in the same case.

CASE (1)

A 6-day old male baby was born to a third degree consanguineously married couple. Antenatal period and delivery of the baby were uncomplicated. Baby cried immediately after birth and apparently looked healthy for 5 days. On day 6th of life the baby was brought to NICU with History of (H/o) refusal of feeds and Yellowish discolouration of the body for -1day. Initially taken it as late onset sepsis. Sepsis work up done -Negative, General Random blood sugar was (GRBS) 62mg/dL and treated with intravenous (i/v) antibiotics and intravenous (i/v) fluids, phototherapy was also given, Blood sample was sent for culture and sensitivity (c/s)- found sterile, Cerebrospinal fluid (CSF) analysis was-normal, the baby improved, feeds were initiated and discharged home, after explaining the mother about danger signs and further follow up visits. At the age of 1 Year, again the child was brought with H/o vomiting for -2 days, immediately after feeds (10-12 episodes), fever for- 2days, hurried breathing and refusal of feeds for-1day. On admission the child had 1episode of convulsion of generalized tonic clonic type. GRBS- was 54mg/dL, blood sample was sent for all other investigations including ABG. Two anticonvulsants were started (as the child not responded to single anticonvulsant) and the convulsions were controlled. On examination (O/E)- signs of dehydration+, tachypnea+, Acidotic breathing+, the child was irritable, delayed motor milestones. Arterial blood gas analysis (ABG) showed-severe metabolic acidosis with anion gap of-34 mmol/L. The child was treated with i/v fluids, i/v antibiotics, dehydration was corrected. Renal Function Test (RFT)/ Liver Function Test (LFT) were- within normal limit, Urine routine examination (URE)- within normal limit, urine for ketone bodies- was negative, blood c/s was-sterile, Ascitic fluid analysis was- normal, CSF analysis-normal, urine for abnormal metabolites- negative, Serum ammonia-305mg/dL, Serum lactate- 35.3mg/dL, Provisional diagnosis of- Organic acidemia (Propionic acidemia) was made. Lipids and dextrose were given with protein restriction, with multivitamins supplements, L-carnitine 100mg/Kg/day and inj. Metronidazole 15mg/Kg/dose was given. Tandem mass spectrometry (TMS) was sent- showed elevated levels Propionyl carnitine, Tetradecanoylcarnitine, Glutaryl carnitine Linoleylcarnitine, Adipylcarnitine, Valine, Leucine/Isoleucine were elevated. Final diagnosis of Propionic acidemia was made. The child was treated symptomatically, improved and discharged home after explaining the mother about danger signs and further follow up visits. Now the child is on syrup Carnitine, syrup Meconerve, tab. Biotin 100mg, syrup Levetiracetam and regular follow up.

CASE (2)

A 9-day old male baby was born to a second degree consanguineously married couple. History of one abortion at 3 months of previous pregnancy. Baby cried immediately after birth and apparently looked healthy for 8 days. On day 9 of life the baby was brought to NICU with h/o refusal of feeds and lethargy for 1day. Initially taken it as late onset sepsis. GRBS-was 56mg/dL, Sepsis work up done -Negative, Blood sample was sent for all other investigations including ABG. Treated with i/v antibiotics and i/v fluids, blood c/s was- sterile, CSF analysis was-normal, baby improved symptomatically, feeds were initiated and discharged home after explaining the mother about danger signs and further follow up visits. At the age of 3months the child was brought with h/o vomiting for 7days, hurried breathing and chest in

Study of Clinical Profile of 5 Cases of Inborn Errors of Metabolism in Critically Ill Children - In Tertiary Care Teaching Hospital Attached to Bangalore Medical College and Research Institute - Bangalore, Karnataka (India). SL Clinical Medicine: Research. 2019; 2(1):114.

drawing for 1 day, excessive crying and refusal of feeds for 1day. On same day of admission, the child had 1episode of convulsion, there was hypoglycemia on admission with GRBS of 42mg/dL, the child was immediately given i/v dextrose 10% 2ml/Kg. Blood sugar level was normalised. But the convulsions were not controlled. Blood sample for serum calcium and other investigations was sent. Later on 2 anticonvulsants were loaded, convulsions were controlled. ABG showed -metabolic acidosis, RFT/LFT- within normal limit, blood c/s was-sterile, CSF analysis was-normal, urine for abnormal metabolites was-negative, Serum Homocysteine levels-normal, Ultrasonography (USG) of abdomen showed-hepatomegaly, Magnetic resonance imaging (MRI) of brain-was normal, 2D echo was done showed- severe Pulmonary arterial hypertension, Serum ammonia-228mg/dL, Serum lactate-64.7 mg/dL. TMS was sent -showed non-specific abnormalities, Branched chain amino acid defect, with elevated levels of leucine. The diagnosis of branched chain aminoaciduria was made. The child was treated with restriction of proteins, i/v antibiotics, i/v fluids, Carnitine 100mg/Kg/day and Thiamine 5mg/Kg/day, the anticonvulsants were continued. Peritoneal dialysis was done but on day 14 of admission the child died due to massive pulmonary hemorrhage.

CASE (3)

A 20-day old female baby was born to a third degree consanguineously married couple. Baby cried immediately after birth and apparently looked healthy for 19 days. There was history of elder sibling death at the age of 1month with similar complaints. Newborn screening (NBS)- was positive for Galactosemia. On day 20th of life the baby was brought to NICU with history of excessive vomiting for 2 days and yellowish discolouration of the body for 16 days (persistent jaundice). Initially taken it as late onset sepsis. GRBS -was 62mg/dL, work up for sepsis done–positive, treated with intravenous antibiotics and i/v fluids. Complete blood count (CBC)- within normal limit, blood c/s was-sterile, Urine culture and sensitivity (c/s)- E.coli (insignificant), Liver function test- slightly deranged (enzymes), USG- abdomen showed-diffuse hepatomegaly, thyroid function test- within normal limit, total bilirubin-7.9mg/dL, direct bilirubin-4.8mg/dL, Retinopathy of prematurity (ROP) screening- Bilateral congenital cataract, Hepatobiliary iminodiacetic acid scan (HIDA scan) was -normal, Prothrombin time/ activated partial thromboplastin time (PT/APTT)- within normal limit, baby started on lactose free milk (Isomil), Vitamin A,D,E,K supplements were given, the baby improved and discharged home after explaining the mother about danger signs and further follow up visits. At the age of 6months the child was again brought with h/o vomiting and loose stools for 4 days, refusal of feeds for 1day. GRBS was-54mg/dL, taken as known case of Galactosemia with some dehydration. The child was treated with i/v antibiotics, i/v fluids and dehydration was corrected. Started on lactose free diet similac and the child was improved and discharged home after counseling the parents regarding the condition. Now the child is on regular follow up visits at our hospital.

CASE (4)

A 3-year old female child was born to a third degree consanguineously married couple. Baby cried immediately after birth. Antenatal, Natal and Postnatal history being uneventful. The child was apparently well till the age of 1year. There is no history of any sibling death in the family. Work up for IEM was not done in the neonatal period. Now the child was brought with history of distension of abdomen for two years, which was gradual in onset, progressive in nature, noted in all quadrants of the abdomen. Swelling in the inguinal region and neck for one week. No history of Cough, cold, fever, edema of feet and hands, convulsions, hematemesis, melena, jaundice, altered sensorium, prolonged drug intake, dyspnea, orthopnea, Nausea, vomiting, anorexia, no history of decreased food intake, recurrent bulky loose stool episodes, swelling of face. Developmental history being appropriate for the age. Immunized up to date. On family pot diet. On general physical examination- Vitals within normal limits, eyes-pallor++, no purpura, Petechiae, no spider nevi over the abdomen, hernial- orifices normal. On per abdominal examination- abdomen protuberant, uniformly distended, umbilicus-transversely stretched, no dilated veins, all quadrants move equally with respiration, no visible pulsations or scars seen. Liver was palpable 5 cms from the right costal margin, with span of 10 cms (hepatomegaly +), smooth surface, rounded border, firm in consistency, Spleen was palpable-below the umbilicus but not below a horizontal line halfway

between umbilicus and pubic symphysis (massive splenomegaly ++), no fluid thrill, no shifting dullness hence no free fluid in the abdominal cavity. Bowel sounds were heard, no bruits, or Venus hum. Other systemic examination being with in normal limits. GRBS was 72mg/dL, CBC- Hemoglobin-4.8gm/dL, severe anemia was noted. Platelet count of 0.55 lakh/cumm (thrombocytopenia +), Peripheral Smear showed-dimorphic anemia with thrombocytopenia, Liver function test- total protein 8gm/dL, albumin 3gm/dL, globulin 3.5gm/dL. Liver enzymes were - within normal limit. Plasma lipid profile showed – hyper triglyceridemia (>500mg/dL), serum uric acid was elevated, Torch profile -with in normal limits. Lymph node biopsy done- showed reactive lymphadenitis. The child was treated symptomatically with antibiotics and analgesics for 1 week. USG abdomen done - hepatomegaly with massive splenomegaly. Liver biopsy: Glycogen storage disorder. So final diagnosis of Glycogen storage disorder was made. The child was given multivitamin and multimineral supplements. Advised mother to give uncooked starch, Tab.clofibrate 500mg (½) /day was prescribed for hypertriglyceridemia, advised mother to reduce fruits in diet, vegetables can be given in enough quantity in the diet. The child improved symptomatically and discharged home after explaining the mother about danger signs and further follow up visits.

CASE (5)

A 4 year 2 months old male child was born to a third degree consanguineously married couple. Baby cried immediately after birth. Antenatal, Natal and Postnatal history being uneventful. The child was apparently well till the age of 4 years and 1 month. No h/o sibling death in the family. Work up for IEM was not done in the neonatal period. Now the child was brought with history of Fever for 1 month, intermittent, mild-moderate grade, on and off, more during the night, associated with chills and rigors, relieved on taking medications and to recur again and afebrile periods in between the fever episodes for few days. Excessive tiredness for 15 days, the child was not able to play like other children of the same age. There is no history of weight loss chronic cough. No history of edema of feet and hands. No history of convulsions, hematemesis, melena, jaundice, altered sensorium, prolonged drug intake, dyspnea, orthopnea, nausea, vomiting, anorexia. No h/o decreased food intake, recurrent bulky loose stool episodes, swelling of face. Developmental history being appropriate for the age. Immunized up to date. On family pot diet. On general physical examination-vitals within normal limits, eyes-pallor++, congestion +, no icterus, no purpura, petechiae, no spider nevi over the abdomen, hernia orifices normal. On per abdominal examination- abdomen protuberant, distension++ more in the right upper quadrant, on left side mass was felt in both upper and lower quadrant, umbilicus-transversely stretched, no dilated veins, all quadrants move equally with respiration, no visible pulsations or scars seen. Liver was palpable 7 cms from the right costal margin, with span of 13 cms (hepatomegaly ++), left lobe was also palpable, smooth surface, rounded border, firm in consistency. Spleen was palpable below the umbilicus but not below a horizontal line halfway between umbilicus and pubic symphysis (massive splenomegaly ++), no fluid thrill, shifting dullness hence no free fluid in the abdominal cavity. Bowel sounds were heard, no bruits or venus hum. Other systemic examination being with in normal limits. GRBS-was 62mg/dL, CBC-Hemoglobin-6.2 gm/dL, Platelet count-0.65 lakh/cumm, Peripheral smear showed- Pancytopenia, Liver function test-total protein 6.3 gm/dL, albumin 2.9 gm/dL, globulin 3.4 gm/dL. Liver enzymes were with in normal limits. Fundus examination was-normal. Peripheral smear for Malarial parasite-negative, widal test -negative, sickling test-negative, Hemoglobin (Hb) electrophoresis-with in normal range. USG abdomen- Splenohepatomegaly and abdominal lymphadenopathy. Bone marrow biopsy was done- showed Abnormal cells, many large cells with abundant cytoplasm, having crumpled tissue paper appearance, suggestive of storage disorder with reduced hematopoiesis suggesting - Gaucher's disease. So final diagnosis of Gaucher's disease was made. Symptomatic treatment was given with multivitamin and multimineral supplements. Blood products transfusion was given. Iron and folic acid supplements were also given. Genetic counselling was done, guided about the enzyme replacement therapy. Child improved symptomatically and discharged home after counseling, is on regular follow up visits.

DISCUSSION

Mortality was seen in 1 out of 5 patients (20%), compared to 28.6% in the study by Jouvet P et al [11]. The incidence of IEM in the population of patients admitted to our PICU was <1% (.66%), a figure quite similar to that previously reported by Ruttimann et al [12]. Where IEM constituted <1% of admissions. All the five children (cases) in our study are born to consanguineously married couple. It is known that parental consanguinity increases the chances of occurrence of autosomal recessive IEM [13]. There is almost no information available on the exact incidence of IEM in PICUs from India. Most IEM present in PICU in a non-specific manner, in form of one of the syndromes (metabolic acidosis, encephalopathy with or without seizures, hepatic presentation, cardiac presentation) [14]. Therefore, in these clinical presentations, IEM should be considered as a possibility and the child should be worked up for IEM with simple biochemical tests, neuroimaging and special tests like TMS and GC/MS. Most of our patients have not been previously worked up for IEM before presenting to our ICU, emphasizing the lack of awareness of IEM among Pediatricians and their non-specific presentation [4].

Our study had certain limitations. The diagnosis of IEM was based on clinical findings, supported by results of tests like blood TMS and urine GC/MS. Though these tests do suggest the diagnosis, final confirmation needs either enzymatic analysis or genetic studies. However, these confirmatory tests for majority of IEMs, are not available in developing countries like India. These confirmatory tests are of utmost importance especially when the clinical picture or the initial findings are not typical. In a given case with typical presenting complaints, clinical findings and neuroimaging/initial biochemical test findings, the results of TMS and urine GC/MS (if suggestive) help in confirming the diagnosis of these conditions. This is very important in IEM, where correct diagnosis helps in proper counseling of parents regarding the prognosis of condition, institution of appropriate dietary measures, use of high dose vitamins and steps to be taken in future when there is deterioration with infections/ stressful situations.

This study also emphasizes the fact that results of sophisticated tests like TMS and GC/MS which are not widely available, can be obtained by collecting samples on filter papers at the time of presentation and then mailing them to higher centers. This is of utmost important in developing countries where in lack of appropriate facilities have led to ignorance about IEM among general Pediatricians. This is also reflected by the paucity of literature on IEM in developing countries. The high mortality rate of IEM presenting in PICU also helps in appropriate counseling of parents when their children are admitted.

Clinical pointers for suspicion of IEM:

Deterioration after a period of apparent normalcy, Parental consanguinity, Family history of neonatal deaths, rapidly progressive encephalopathy and seizures of unexplained cause, Severe metabolic acidosis, Persistent vomiting, Peculiar odor, Hemolysis, elevated liver enzymes & low platelet counts (HELLP) - during pregnancy: seen in women carrying foetuses with long-chain-3-hydroxyacyl-coenzyme dehydrogenase deficiency.

First line investigations (metabolic screen):

(1) Complete blood count (CBC): (neutropenia and thrombocytopenia seen in propionic and methyl malonic acidemia)

(2) Arterial blood gas analysis (ABG)

(3) Serum electrolytes

(4) Blood glucose (GRBS)

(5) Plasma ammonia

(6) Arterial blood lactate

(7) Liver function test

(8) Urine ketones

(9) Urine reducing substances

(10) Serum uric acid

Categorization of Neonatal IEM using metabolic screening tests:

Acidosis	Ketosis	↑ Lactate	↑ Ammonia	Diagnosis
-	+	-	-	Maple syrup urine disease
+	+/-	-	+/-	Organic aciduria
+	+/-	+	-	Lactic acidosis
-	-	-	+	Urea cycle defect
-	-	-	-	Non-Ketotic hyperglycinemia, Peroxisomal disorders, Phenylketonuria, Galactosemia

Study of Clinical Profile of 5 Cases of Inborn Errors of Metabolism in Critically Ill Children - In Tertiary Care Teaching Hospital Attached to Bangalore Medical College and Research Institute - Bangalore, Karnataka (India). SL Clinical Medicine: Research. 2019; 2(1):114.

Second line investigations (confirmatory tests):

1. Gas chromatography mass spectrometry (GCMS) of urine: Diagnosis of organic acidemias.
2. Plasma amino acids and acyl carnitine profile: TMS- for diagnosis of organic acidemias, urea cycle defects, aminoacidopathies and fatty acid oxidation defects.
3. High performance liquid chromatography (HPLC): Quantitative analysis of amino acids in blood and urine; required for diagnosis of organic acidemias and aminoacidopathies.
4. Lactate/pyruvate ratio- in cases with elevated lactate
5. Urinary orotic acid: In cases with hyperammonemia for classification of urea cycle defect.
6. Enzyme assay: This is required for definitive diagnosis like GALT (galactose 1- phosphate uridyl transferase) assay- in cases with suspected galactosemia
7. MRI: Agenesis of corpus callosum has been reported in Menke's disease, pyruvate decarboxylase deficiency, MSUD- Maple syrup urine disease and non-ketotic hyperglycinemia [15]. Propionic & methyl malonic acidemia: basal ganglia signal change Glutaric aciduria: frontotemporal atrophy, subdural hematomas.
8. Electroencephalography: Comb-like rhythm in Maple syrup urine disease (MSUD), burst suppression in Non-ketotic hyperglycinemia (NKH) and holocarboxylase synthetase deficiency [16].
9. Magnetic resonance spectroscopy- lactate peak elevated in mitochondrial disorders and leucine peak elevated in MSUD.

Genetic counselling and prenatal diagnosis: Most of the IEM are single gene defects, inherited in an autosomal recessive manner, with a 25% recurrence risk. Therefore, when the diagnosis is known and confirmed in the index case, prenatal diagnosis can be offered, wherever available for the subsequent pregnancies. The samples required are chorionic villus tissue or amniotic fluid [17]. Modalities available Are- Substrate detection: Useful in phenylketonuria, peroxisomal defects. Enzyme assay: In Niemann-Pick disease, Gaucher disease. DNA based diagnosis: Detection of mutation in proband / carrier parents.

Aims of treatment: 1. To reduce the formation of toxic metabolites by decreasing substrate availability.

2. To provide adequate calories

3. To enhance the excretion of toxic metabolites.

4. To institute co-factor therapy for specific disease and also empirically if diagnosis not established

5. Supportive care-treatment of seizures maintain euglycemia and normothermia, fluid, electrolyte & acid-base balance, treatment of infection, mechanical ventilation if required.

Long term treatment of IEM:

1. Dietary treatment- Special diets are available for IEM but are very expensive and cannot be afforded by most of the Indian patients. Based on the amino acid content of some common food products are available in India.

2. Enzyme replacement therapy (ERT)- Is now commercially available for some Lysosomal storage disorders [18]. However, disorders do not manifest in the newborn period except Pompe's disease which may present in the newborn period and ERT is now available.

3. Cofactor replacement therapy- Thiamin, Riboflavin, Pyridoxine, Cobalamin, Folinic acid, Biotin.

CONCLUSION

One of the cases in our study was presented with features suggestive of late onset sepsis, persistent vomiting, breathlessness, fever, convulsion and delayed motor milestone was diagnosed as Propionic acidemia. One more child was presented with features suggestive of late onset sepsis, refusal of feeds and lethargy, hurried breathing and chest in drawing with history of 1 abortion at 3 months in previous pregnancy, on proper investigation the child was diagnosed as Branched chain aminoaciduria. The other child was presented with excessive vomiting and persistent jaundice, NBS was positive for Galactosemia and history of elder sibling death at the age of 1 month having similar features was found to be Galactosemia after thorough work up. A female child was presented for the first time at the age of 3 years having distension of abdomen, Splenohepatomegaly for 2 years, was diagnosed to be Glycogen storage disorder after the liver biopsy was done. A 4-year 2 months old male child was presented for the first time with features of distention of abdomen, massive splenomegaly, Pneumonia and

Study of Clinical Profile of 5 Cases of Inborn Errors of Metabolism in Critically Ill Children - In Tertiary Care Teaching Hospital Attached to Bangalore Medical College and Research Institute - Bangalore, Karnataka (India). SL Clinical Medicine: Research. 2019; 2(1):114.

Pancytopenia was found to be suffering from Gaucher's disease when we had done bone marrow biopsy which showed typical features suggestive of Gaucher's disease.

Early diagnosis of the condition by various laboratory tests and initiation of prompt therapy is very much essential in order to prevent lethal complications which are irreversible. Inborn error of metabolism should be considered in children presenting with features mimicking sepsis, Hypoxic ischemic encephalopathy and other perinatal events. Diagnosis is important not only for the treatment but also for genetic counselling and antenatal diagnosis in subsequent pregnancies.

Though IEM may not appear as a large number, yet it is significant as many of them will present with critical illness and many of them will survive with lot of neurological damage. Screening programmes and prenatal diagnosis of IEM will go a long way in prevention and in genetic counselling. This would benefit the society as a whole in reducing and preventing psycho-social burden of the medical consequences due to IEM. The concept that "genetic disorders are very difficult to diagnose and if diagnosed, it is impossible to treat" no more stands.

RECOMMENDATIONS

1. TMS-is used in some countries including India for Newborn screening, it should be made available in all districts of our state, free of cost to all patients if possible.

2. Infants who screen positive should undergo further confirmative testing so that the baby was truly affected with the disease or the test result was false positive.

3. Follow-up testing is typically co-ordinated between geneticists and the Pediatrician or primary care physician.

4.Prenatal and Newborn screening to identify infants with treatable metabolic disorders before they present clinically or suffer irreversible damage, help to reduce societal burden as well as the mortality and morbidity due to IEM.

5. The most important is to get the government's policy and financial support for expanded screening procedures. However, success of any screening programme requires public participation.

ACKNOWLEDGEMENT

We sincerely acknowledge all the children and their parents who have participated in our study. We also acknowledge all the Staff members and Post graduate students of Vanivilas hospital, Bowring and Lady Curzon hospital, Bangalore for their kind co-operation.

REFERENCES

1. Choudhuri T, Sengupta S. (2006). Inborn error of metabolism-an Indian perspective. Int J Human Genet. 6: 89-91.
2. Childs B, Valle D, Jimenez-Sanchez. (2001). The inborn error and biochemical variability. In: Scriver CR, Beaudet AL, Sly WS, Valle D (Eds.), The metabolic and molecular bases of inherited disease, 8th edn. New York: Mc-Graw Hill. 155-166.
3. Oliveira AC, Nunes AM, Santos d, Martins AM, D'Almeida V. (2001). Screening for Inborn errors of metabolism among newborns with metabolic disturbance and/or neurological manifestations without determined cause. Sao Paulo Med J. 119: 160-164.
4. Kumta NB. (2005). Inborn errors of metabolism (IEM) -- an Indian perspective. Indian J Paediatr. 72: 325-332.
5. Bhatt C, Misra Z, Goyel N. (2008). Detection of inherited metabolic diseases in children with mental handicap. Indian J ClinBiochem. 23: 10-16.
6. Verma IC. (1986). Genetic disorders need more attention in developing countries. World health forum. 7: 69-70.
7. Verma IC, Bijarnia S. (2002). The burden of genetic disorders in India and a framework for community control. Community genetics. 5: 192-196.
8. Verma IC, S Bijarnia, RatnaPuri. (2006). Burden of genetic disorders in India, Preventive genetics, editor Sharad Gogate. 36-46.
9. Jalan AB. (2000). Inborn Error of metabolism in critically ill newborn Part I Perinatology. 3: 13-24.
10. Jalan AB. (2000). Inborn Error of metabolism in critically ill newborn Part I Perinatology. 3: 113-121.
11. Jouvet P, Touati G, Lesage F, Dupic L, Tucci M, et al. (2007). Impact of inborn errors of metabolism on admission and mortality in a pediatric intensive care unit. Eur J Pediatr. 166: 461–465.
12. Ruttimann UE, Patel KM, Pollack MM. (2000). Relevance of diagnostic diversity and patient volumes for quality and

length of stay in pediatric intensive care units. Pediatr Crit Care Med. 1: 133–139.

13. Rao AN, Koch M, Kavitha J, Ghosh S, Kumar SV. (2008). Consanguinity and inborn errors of metabolism- an early impression Prevalence and counseling. Perinatology. 10: 75-83.
14. Clarke JTR. (2006). A clinical guide to inherited metabolic diseases. 3rd edn. Cambridge: Cambridge University Press. 1-27.
15. Blaser S, Feigenbaum A. (2004). A neuroimaging approach to Inborn Errors of metabolism. Neuroimag Clin N Am. 14: 307-329.
16. Nordli DR, De Vivo DC. (2002). Classification of infantile seizures: Implication for identification and treatment of Inborn Errors of metabolism. J Child Neurol. 17: 353-358.
17. Elias S, Simpson JL, Shulman LP. (2002). Techniques for prenatal diagnosis. In: Rimoin DL, Connor JH, Pyeritz RE, Korf BR, editors. Emery and Rimoin's Principles and practice of medical genetics Churchill-Livingstone, London. 802-825.
18. Brady RO, Schiffman R. (2004). Enzyme- replacement therapy for metabolic storage disorders. Lancet Neurol. 3: 752-756.