ORIGINAL RESEARCH

Clinical and laboratory profile of Inherited Metabolic Disorders in children at a tertiary care Centre

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ABSTRACT

Background: Inborn errors of metabolism are group of disorders due to one or more defective or nonfunctional enzymes or defect in transport of proteins. Asymptomatic newborn with IEM can later present with irreversible neurological damage, hence NBS is widely accepted in developed countries. In contrast, less information is available from developing countries. In view of paucity of reports on clinical presentation and basic metabolic workup in our country, we made an attempt to study the clinical and laboratory profile. **Methodology;** Study was a cross sectional observational study, consisting of 50 participants who were screened for Inherited Metabolic Disorders based on clinical features and significant preliminary laboratory findings by tandem mass spectrometry using their dried blood samples. Clinical and laboratory profile of diagnosed metabolic disorders were recorded. **Results**; Common clinical manifestations were seizures, poor feeding and vomiting. There was significant association with consanguinity, developmental delay and recurrent abortions. Signs of encephalopathy and organomegaly were common clinical finding. Abnormal blood gases and serum lactate were usual laboratory results. Of 50 cases fatty acid oxidation and mitochondrial disorders were major contributors. Of 50 children, 25 succumbed with fatty acid oxidation being major killer. **Conclusion**; Inherited metabolic diseases are not uncommon and diagnosis needs a high index of suspicion. Early diagnosis and treatment may be able to save a number of these children hence there is need to develop local facilities to establish the diagnosis. Further, there is need for neonatal screening programs in developing countries like India for early diagnosis and treatment.

Keywords: Inborn errors of metabolism (IEM); Encephalopathy, seizures

INTRODUCTION

Inborn errors of metabolism are the hereditary diseases which occur due to disturbances in normal biochemical process. Although individual diseases are rare, they collectively cause significant amount of morbidity and mortality.

Inborn errors of metabolism are group of disorders due to one or more defective or nonfunctional enzymes or defect in transport of proteins. The defective enzyme disturbs the metabolic reaction that leads to deficiency of essential products for cell function, accumulation of substrates or toxic metabolites of alternative pathway. IEMs are congenital chemical alterations, also called as Inherited Metabolic Disorder (IMD). These are individually rare with average incidence of 1 in 100000. But due to huge number of enzymatic derangements, they are collectively common with overall incidence of 1 in 800 to 1 in 2500. They are one of the major contributorsto chronic diseases in childhood.[1]

Clinical manifestations depend on the concentrations of accumulated toxic metabolites. As a consequence of this, IEM may be exhibiting severe symptoms or

may be asymptomatic. Frequently manifested symptoms which suggest that IEM may fall into several categories including hypoxia, seizures, lethargy, vomiting, poor feeding and other changes that may often cause death if not promptly intervened.[2] Asymptomatic individuals become symptomatic following exposure to triggers such as fasting, diet, fever, drugs, anesthesia.

Prompt diagnosis is required even in asymptomatic individuals to prevent sequalae. Proper diagnosis requires the use of biochemical markers, and the diagnosed cases may require lifelong therapy, so it imposes a substantial burden on the patient's family which includes cost of diagnosis and treatment.[3]

One single test is not enough to identify the IEM. Different strategies are required to diagnose it. Accumulated biochemical substances can be estimated in blood or urine. Knowledge of analytical chemistry, enzymology and biochemistry helps to plan final work of IEM. To improve the establishment of diagnosis and management of long-term effects Newborn screening (NBS), gas chromatography massspectrometry (GCMS), tandem mass spectrometry (TMS), molecular analysis and enzyme assay has been developed. With the above diagnostic techniques, the numbersof patients diagnosed with IEM are at a rise.Some of them are responsive to therapy if treatment is started early. In case where the therapy is unavailable diagnostic methods will be useful for genetic and prenatal counselling. Asymptomatic newborn with IEM can later present with irreversible neurological damage, hence NBS is widely accepted in developed countries In contrast, less information is available from developing countries.[4]

MATERIALS AND METHODS

Study was a cross sectional observational study of children who were admitted in two hospitals i.e., Chigateri General Hospital and Bapuji Child Health Institute, Davangere with suspected metabolic disorder. Children included in the study were those with history of undiagnosed early neonatal death in siblings, persistent jaundice, convulsions, hypotonia, respiratory distress, persistent vomiting for which no infection or surgical cause is identified. Children admitted with unexplained neurological deterioration following infection, persistent acidotic breathing, unexplained coma/focal deficits and positive family history of known or suspected IMD were included in the study. These were screened for Inherited Metabolic Disorders by tandem mass spectrometry, using their dried blood samples. Children with proven sepsis and others with known cause for neurological deterioration were excluded from the study.Clinical and laboratory profile of these children with IMD and their outcome were recorded in this study.

Informed consent from parent/guardian was obtained. Detailed information collected including various patient demographic characteristics including family history, presenting complaints, growth and development. Relevant clinical examination findings were documented.

Initial investigations included complete blood count, blood sugar, renal function test, liver function test, arterial blood gas analysis, serum ammonia, lactate. To confirm the diagnosis, Bone marrow examination, Tandem Mass Spectroscopy, Gas Chromatography, urine organic acid levels, liver biopsy and genetic analysis, imaging were done depending on clinical correlation and availability of diagnostic tools. All the above data were entered in a pre-structured Proforma.

Ethical consideration

This study does not include any experimentation. Patients are informed of the procedure done in detail and informed consent is obtained. No one received any benefit, personal or professional from a commercial party directly or indirectly including the objective of this study.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) version 20. [IBM SPSS statistics (IBM corp. Armonk, NY, USA released 2011)] was used to perform the statistical analysis. Data was entered in the excel spread sheet. Descriptive statistics of the explanatory and outcome variables were calculated by frequency and proportions for qualitative variables.

RESULTS

Table1: Age Distribution

Age group	Frequency	Percent
< 1year	24	48.0
1 - 5 years	19	38.0
5 - 10 years	2	4.0
10 - 15 year	5	10.0
Total	**50**	**100.0**

In our study, age group of <1 year contributed 48%, 1-5 years contributed 38%, 5-10 contributed 4% and 10-15 years contributed 10%. In our study, male children constituted 60% and 2% were ambiguous.

Table 2: Family history

	Frequency	Percent
Consanguinity	41	82.0
Unexplained neonatal or infant death in family	6	12
Diagnosed case of IMD in family	4	8
Recurrent Abortions	15	30

Consanguineous marriage and recurrent abortions were predominant findings.

Table3: Presenting Complaints

Complaints	Frequency	Percent
Poor feeding	13	26.0
Vomiting	10	20.0
Failure to thrive	8	16.0
Lethargy	8	16.0
Seizures	29	58.0
Jaundice	5	10.0

Seizures was the commonest presenting complaint.

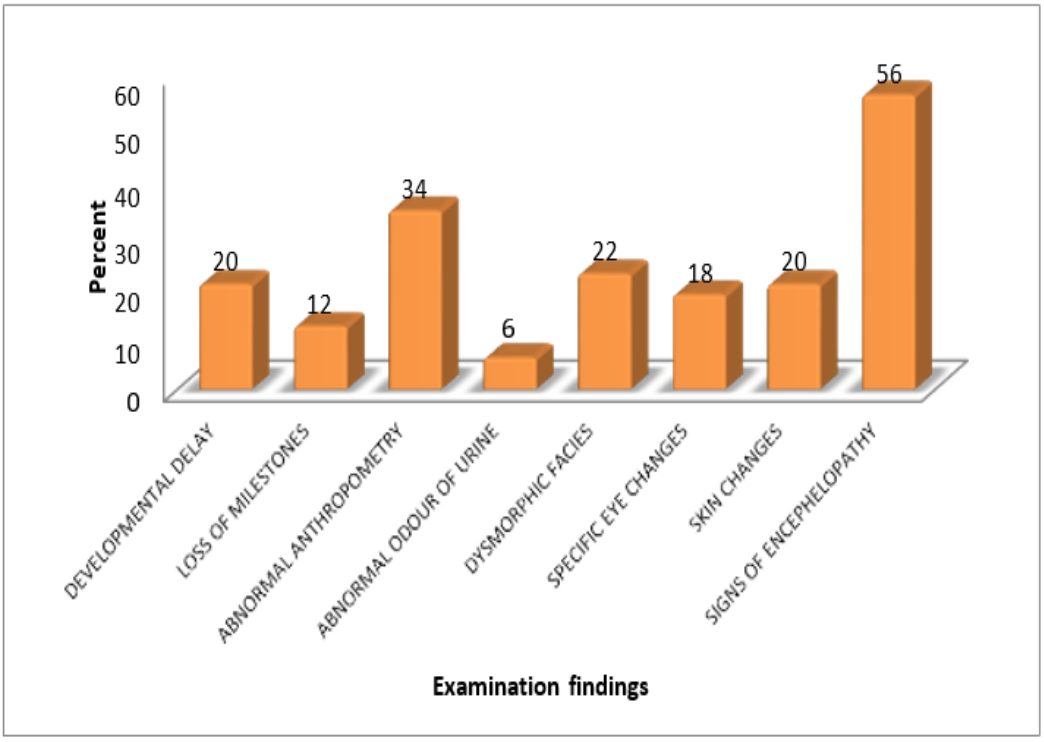

Figure1: Examination Findings

Encephalopathy and abnormal anthropometry were predominant clinical findings
Though investigations relevant were done based on suspected etiology abnormal ABG and abnormal TMS were common findings.

Table 4: Laboratory findings

Abnormal	Frequency
ABG	25
S. Ammonia	10
S. Lactate	17
USG	21
MRI	16
TMS/GCMS	22

In our study, fatty acid oxidation disorder was major contributor in the study population.

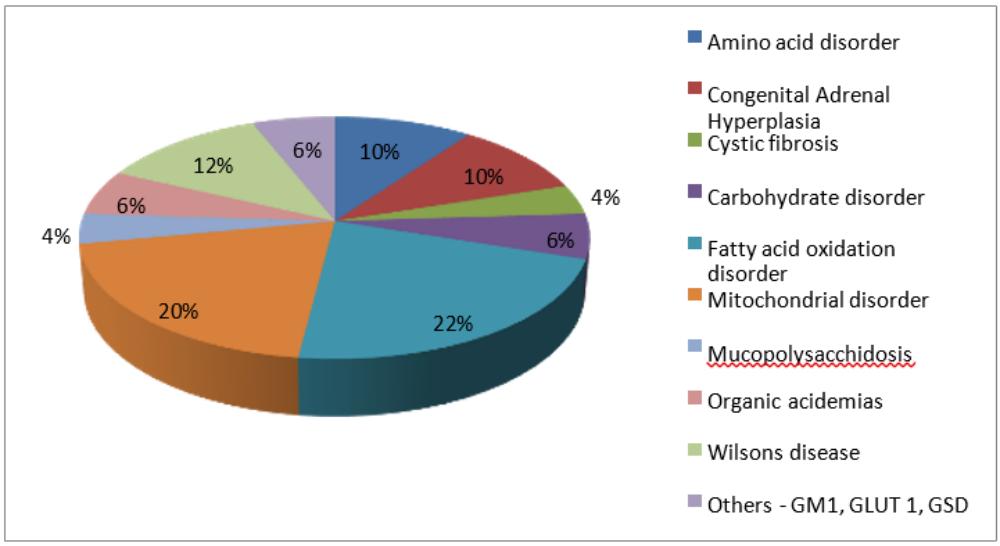

Figure 2: Diagnosis

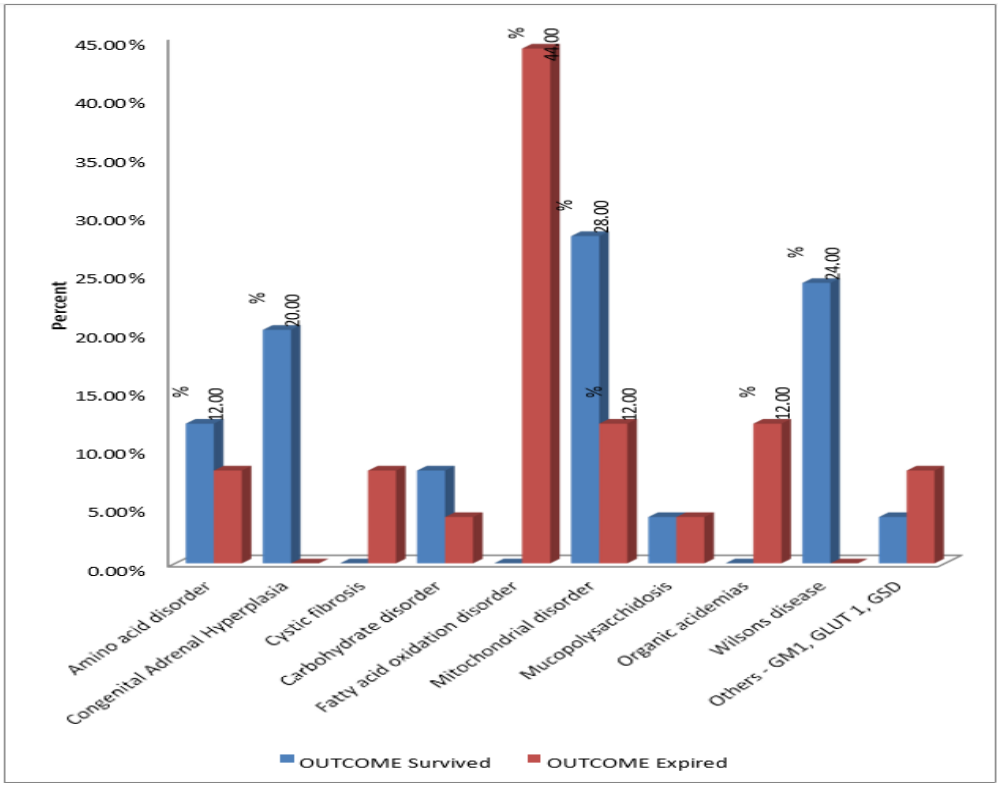

Figure3: Outcome – Diagnosis

In our study fatty acid oxidation disorder was major contributor for mortality.

DISCUSSION

In India the occurrence of IEM is not exactly known. This may be due to lack of studies on IEM based on large population or studies are done only on a selected population. In view of paucity of reports on clinical presentation and basic metabolic workup in our country, we made an attempt to study the clinical and laboratory profile.

In our study total of 50 cases were taken for analysis. Large numbers presented in **infancy**. Majority of patients were **males c**onstituting about 60% of the study population. This is quite similar to study by Jailkhani, Rama, Patil*et al.*,[5] from Karnataka. Many national and international studies in IEM also reported male affection.

Ramaswamy Ganesh *et al.*,[6] did a study in clinical profile and outcome of children with Inborn errors of metabolism over a period of 1 year from June 2017 to May 2018. According to that 31 newly diagnosed patients were studied for clinical, biochemical and diagnosis, 65% were born to consanguineous parents. In our study, 82% were born out of consanguineous marriage.

Analysis of history which included complaints, family history, consanguinity and physical signs were used to decide about metabolic workup. **Family history** revealed consanguinity in 82% of cases and history of recurrent abortions in 30%. As most of the IEMare autosomal recessive, chances of recurrence of the disorder are 25% in cases with history of sibling affection. Consanguinity rate is high in South India and hence increases the chances of IEM.

Suvasini Sharma *et al.*,[7] observed developmental delay, regression of mile stones, behavioral impairments, seizure are more common clinical presentation with IEM. Jean – Marie Sau Dubray *et al.*,[8] done a study titled an overview of inborn errors of metabolism affecting the brain: from neuro development to neurodegenerative disorders. They stated that 85% display predominantly neurological manifestations. Neurodevelopment is constantly disturbed in the neurological presentations of IEMs. The precise neurobiological stage of developmentthat is affected are particular to every IEM. Additionally, neurodevelopment and neuro degeneration can behave as opposites throughout disease evaluation, but they are parallel.

Our study supports the **clinical manifestations** similar to that. Seizure observedin 58% of children, encephalopathy in 56%, abnormal anthropometry in 34% poor feeding in 28%, developmental delay in 20% of children. Data revealed that most common symptom at presentation was seizures. Though failure to thrive as a presenting complaint was less significant children had abnormal anthropometry.

In a study by Meow Keong Thong *et al.*,[9] selected testing of all ill infants and children for IEM yielded 2% positive results. Out of 264 patients the **spectrum of IEM** included 98 were organic acidurias, 78 amino acidopathies, 54 urea cycle disorders, 12 neurotransmitter conditions, and lysosomal disorders. In this study they reviewed the epidemiology and the spectrum of IEM from 1999 to 2005 in making the diagnosis of IEMs from patients suspected to have IEM. That was served as a directionfor primary prevention of IEM in the community.

A retrospective study by Ananth Rao *et al.*,[10] reviewed 869 cases which referred from several diagnostic centers and hospitals. Data analyzed indicates occurrence of several metabolic disorders in our population.

In our study, fatty acid oxidation defect, congenital adrenal hyperplasia and mitochondrial disorders were major contributors who had significant morbidity and mortality. Diagnosis of these conditions in early life would have given better survival opportunity. Early and accurate diagnosis will reduce the mortality for some diseases, help for prenatal diagnosis and genetic counselling for next pregnancy. Limitations of this study is that it was a hospital-based study which is not strictly representative of the background population. Enzymes assay for storage disorders, molecular genetic testing, next generation gene sequencing, mutation analysis not done in many of the cases due to non-availability and financial constraints.

The need to screen for inborn errors metabolism arises out of the fact that most cases take to irreversible effects as time progress. Early diagnosis and prompt management needed to alleviate symptoms and prevent complications.

CONCLUSION

Inherited metabolic diseases are not uncommon and diagnosis needs a high index of suspicion.Early diagnosis and treatment may be able to save a number of these children hence there is need to develop local facilities to establish the diagnosis.Further, there is need for neonatal screening programs in developing countries like India for early diagnosis and treatment.

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Competing Interests: None

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