Inborn Errors of Metabolism in Newborns: An Experience of Tertiary Care Hospital in Islamabad

Syeda Shireen Gul¹, Ayesha Isani Majeed², Abida Faiz Talpur³

ABSTRACT

Objective: To determine the frequency of inborn error of metabolism in clinically suspected neonates and to determine the frequency of clinical presentations among them through Tandem Mass Spectrometry

Study Design: Cross-sectional observational study

Place & duration of study: Neonatology unit of PIMS, Islamabad from January 2016 to January 2017.

Methodology: A total of fifty-five (n=55) neonates with history of undiagnosed early neonatal death in the siblings or unexplained persistent jaundice, convulsions, hypotonia, respiratory distress, persistent vomiting were enrolled in the study. Screening for inborn errors of metabolism was done by the tandem mass spectrometry using their dried blood samples.

Results: 30 (54.5%) out of 55 total patients were positive for inborn errors of metabolism. 20 (66.66%) of the positive patients were male while 10 (33.33%) were females. Most common clinical presentation followed by persistent jaundice found to be the vomiting. From all the positive cases, 19 (63.33%) had a history of the death of siblings with similar complaints. 22 (73.33%) neonates were the product of consanguineous marriage, 08 (26.66%) neonates had a G6PD deficiency, 10 (33.33%) had disorders of amino acid metabolism, 4 (13.33%) had congenital adrenal hyperplasia, 3(10%) had Cystic fibrosis, 2 (6.66%) had organic acidemias and 3 (10%) had disorders of carbohydrate metabolism.

Conclusion: A significant percentage of clinically suspected neonates found to have inborn errors of metabolism in this study. Errors in amino acid metabolism being highest in the list followed by G6PD Deficiency. The commonest presentations were vomiting followed by persistent jaundice.

Key Words: Neonates, Tandem Mass Spectrometry, inborn errors of metabolism.

Introduction

Inborn errors of metabolism (IEM) are single gene disorders resulting from the defects in the biochemical pathways of the body.¹ This leads to both abnormal synthesis as well as catabolism of metabolites. Most of these metabolites are neurotoxic and may cause death in early neonatal period or severe neurological disability.² Although these disorders are individually rare, collectively they account for a significant portion of childhood disability and deaths. The prevalence of IEM in different countries varies between 1 in 800 to 1 in 5000 neonates.³ ²⁴ The overall incidence of recorded IEM was 10-fold greater among Pakistani children compared to white children. Most of the IEMs are inherited disorders, caused by genetic mutations leading to defective protein function. Most are inherited in autosomal recessive pattern and few are X-linked recessive disorders.⁵ In Pakistan, it is reported that more than half of all marriages (56%) are between first and second cousins. Consanguinity increases the risk of these rare genetic recessive disorders.⁶ The clinical signs and...
symptoms arise from the accumulation of the toxic substrates, deficiency of the product, or both. Hundreds of disorders have been described until now and there has been a considerable clinical overlap between certain inborn errors and definitive diagnosis depends on enzyme assays or genetic tests.\textsuperscript{7} In recent years, neonatal mass screening for organic acidemia, fatty acid disorders and other such similar metabolic disorders is being seriously considered in several places throughout the world and tandem mass spectrometry or gas chromatography-mass spectrometry (MS/GC) are being used.\textsuperscript{8,9} Patients with such disorders can have acute symptoms such as lethargy, hypotonia, tachypnea, convulsions, vomiting or may present with developmental delay or mental retardation and could die of 'obscure causes' despite the fact that a number of such patients could potentially achieve normal growth and development if early detection and intervention were feasible.\textsuperscript{10}

Early detection and treatment of an IEM are important. The child with IEM often deteriorates suddenly and progresses rapidly with severe permanent brain damage. Treatment is effective if started early and the earlier return of metabolic stability correlates well with long-term prognosis and prevents learning handicap.\textsuperscript{11} There are not much studies conducted in local population on the subject likely due to the unavailability of diagnostic tools at primary or secondary care health facilities. Purpose of present study is to find out the burden of disease in northern region of Pakistan and to study the spectrum of clinical presentation. This will help in scrutinize the neonates for early screening as significant number of such patients could potentially achieve normal growth and development if early detection and intervention are feasible. Clinicians will also be able in counselling the family before the next child is conceived. Prenatal diagnosis can also be offered as an alternative reproductive option if the genotype or enzyme defects are known.

Our objective was to determine the frequency of inborn error of metabolism in clinically suspected neonates and to determine various clinical presentations among them through Tandem Mass Spectrometry.

**Methodology**

It was a cross-sectional observational study conducted at the neonatology department of Pakistan Institute of Medical Sciences during January 2015 to January 2016. A total of fifty-five (n=55) neonates with history of undiagnosed early neonatal death in the siblings, persistent jaundice, convulsions, hypotonia, respiratory distress, persistent vomiting for which no infection or surgical cause was identified were enrolled in the study. Screening for inborn errors of metabolism was done by the tandem mass spectrometry using their dried blood samples. Blood complete picture, renal and liver function tests, serum electrolytes, anion gap, C-reactive protein, PT/APTT, cultures of blood, cerebrospinal fluid (CSF) and urine, arterial blood gas analysis, serum ammonia and lactate, urine ketones and reducing sugar analysis were done according to the relevant presenting complaints and examination findings. Neuro-imaging was done as indicated in neonates with seizures and coma to help in the diagnosis. If laboratory findings were significant or no cause of the presenting features were found then dried blood samples (DBS) were sent to IEM screening unit in Jordan. Dried blood sampling was relatively simple and is done by collecting few drops of blood of about 3 mm in diameter on specialized filter paper (Guthrie card) of size 12cm x 8cm. Dried blood analysis included: TSH levels, IRT levels for cystic fibrosis, 17-hydroxyprogesterone levels for congenital adrenal hyperplasia, Galactose levels for Galactosemia, G6PD activity for G6PD deficiency, Hemoglobinopathies, Amino Acid disorders including Phenylketonuria, maple syrup urine disease, Homocystinuria, tyrosinemia, citrullinemia, Arginosuccinic aciduria. Organic acid disorders including Malonic aciduria, Isovaleric aciduria, Propionic aciduria, methylmalonic aciduria. Fatty acid disorders including Medium Chain Acyl Co-A dehydrogenase deficiency, short chain Acyl Co-A dehydrogenase deficiency, Glutaric Acidemia type II, Carnitine uptake deficiency, Trifunctional protein deficiency, Very long chain Acyl Co-A dehydrogenase deficiency.

**Results**

A total of 55 neonates from 1st day of life till 28th day of life were finally included in the study after as per our inclusion criteria. Age and gender distribution is represented in table I. A total of 54.5% (n=30/55) were tested positive for a specific metabolic disorder in this study. Inborn errors of Amino acid metabolism being highest in the list followed by G6PD Deficiency (table II). Disorders of amino acid metabolism included Tyrosinemia, citrullinemia, Homocystinuria, Maple syrup urine disease, Phenylketonuria and Arginosuccinic aciduria were found in 3.33, 6.66, 3.33, 6.66, 10%, 3.33 % neonates respectively. The commonest presentations were vomiting followed by persistent jaundice.
Male predominance was noted among disease positive neonates with the result 20 (66.66%) male and 10 (33.33%) female (P<0.05). History of Early neonatal deaths was positive in 19 (63.33%) cases while history of consanguous marriage was positive in 22 (73.33%) neonates.

Table I: Distribution of age and gender in the study sample

<table>
<thead>
<tr>
<th>GENDER</th>
<th>Frequency (percentage)</th>
<th>Mean Age in days ± (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALES</td>
<td>23 (42%)</td>
<td>16.4</td>
</tr>
<tr>
<td>FEMALES</td>
<td>32 (58%)</td>
<td>12.8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>55</td>
<td>14.1 (3.1)</td>
</tr>
</tbody>
</table>

Table II: Inborn errors of metabolism in study sample

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Errors of Amino acid metabolism</td>
<td>10</td>
<td>33.3</td>
</tr>
<tr>
<td>G6PD Deficiency</td>
<td>8</td>
<td>26.7</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>4</td>
<td>13.3</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Disorders of carbohydrate metabolism</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Organic acidemias</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>100</td>
</tr>
</tbody>
</table>

Table III: Clinical presentation spectrum in study sample

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>Persistent jaundice</td>
<td>10</td>
<td>33.3</td>
</tr>
<tr>
<td>Seizures</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Reluctance to feed</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Difficulty in breathing</td>
<td>5</td>
<td>16.7</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>2</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Discussion

Metabolic disorders are group of inherited disorders that cause significant morbidity and mortality. Archibald Garrod in 1909 introduced the concept of IEM. These are congenital metabolic disorders, caused by genetic mutations leading to defective protein function, resulting in the absence or abnormality of an enzyme or cofactor, causing either accumulation or deficiency of a specific metabolite. The outcome depends upon recognition of the signs and symptoms, timely evaluation, and transfer to a facility which is familiar with the evaluation and comprehensive testing along with the experience of management of these disorders. Any delay in diagnosis can lead either early death or significant morbidity in the form of neurological deficit. Majority of severe forms of metabolic disorders present in childhood. Most pediatricians have to face these disorders; hence they should have experience in diagnosing and treating these diseases. Moreover, improved and available treatments which include enzyme replacement therapy (ERT), toxic substrate inhibitors and diet restrictions have changed the prognosis of some of these diseases. Possible improved outcome increases the importance of recognizing these disorders.

In this study, 55% of clinically suspected neonates were found to have metabolic disorders. Individual IEM are rare disorders, most having reported the incidence of less than 1 per 100,000 births. However, the incidence may approach 1 in 800 - 2500 births when considered collectively. Incidence of metabolic diseases in Pakistan is not known. In studies from Pakistan, IEMs were confirmed in 5/10 (50%) cases at the Shifa International Hospital, Islamabad, and in 16/62 (26%) cases at National Institute of Child Health, Karachi. In a study from India, 869 cases were screened among whom 2.65% were diagnosed to be having specific IEM.

In the present study, consanguinity rate was present in 73.33%. This is comparable to a study from Libya where consanguinity was observed in 69%. In this study, inborn errors of Amino acid metabolism was the commonest disorder in the studied population which was found in 33.33% cases followed by G6PD Deficiency 26.66%, and Cystic fibrosis 10%. In contrast, the frequency of 6.13%, 22%, and 1%, respectively have been reported of these disorders by variously published researches.

In Pakistani population, owing to high rate of intermarriages and large family size, our assumption that these metabolic disorders including rare disorders, all are prevalent in Pakistan, seems to be true. The diagnosis of inherited metabolic disorders has increased in recent years in our country. Some centers have initiated work-up and management of these disorders. But there is a lack of therapeutic and diagnostic resources, including metabolic laboratories, confirmatory DNA testing, specialist in this field, and specialized metabolic dietitian. For this study, the authors had to send samples for diagnostic work-up to a laboratory in another country. Most of diagnoses were made on the basis of enzyme assay and substrates analysis, whereas, genetic mutations are not being done. We did not gather data for the type of mutations prevalent in this study.
population. Gene analysis has significantly improved prenatal diagnosis and identification of healthy heterozygotes, thus significantly improving importance and application of genetic counselling.\textsuperscript{20} Without knowledge of these mutations, antenatal diagnosis is not possible. In the last decade, introduction of tandem mass spectrometry has expanded newborn screening (NBS). Now, this programme is mandatory in most of the developed and developing countries as a public health strategy.\textsuperscript{21} In Pakistan, a comprehensive neonatal screening program is rarely available. There is a need of creating local facilities for diagnosing these disorders and awareness of primary as well as tertiary care level for proper referral, as most cases of crisis are treated as sepsis, mental retardation and cerebral palsy, and there is no further evaluation and proper management. This study provides valuable information for future metabolic newborn screening program, which is treatable; and most frequent metabolic disorders should be considered for screening. To treat acute and life-threatening cases in the treatment of metabolic disorders, the priority was given to manage intoxication. However, the treatment for lysosomal diseases like Gaucher’s disease and MPS, where enzyme replacement therapy is available and in vogue, pediatricians should make themselves familiar with these sophisticated regimens.\textsuperscript{22} Dietary management is essential for metabolic disorders. Dietitians in association with metabolic specialists should make plans for protein restricted or modified diet for these patients and must provide adequate nutrition to them. Diets normally consist mainly of special medical milk formulas for specific disorders and selective natural foods. Cost, unavailability of drugs, poor medical and nutritional compliance reduce the efficacy of treatment in population of developing countries. Inherited metabolic disorders were not only common in first cousin marriages but also in non-cousin marriages of the same caste. Arian was the most commonly affected caste showing IEM.

In summary, there is a need to create local awareness of inborn errors of metabolism at primary as well as tertiary care levels as most of the cases remain undiagnosed. There should be a proper referral of suspected cases for further evaluation and management. Our study provides valuable information about the common presenting features of suspected IEM and risk factors and the benefit of Tandem Mass Spectrometry. Most frequent disorders should be considered for screening in at-risk children.

---

**Conclusion**

A significant percentage of clinically suspected neonates found to have inborn errors of metabolism in this study. Errors in amino acid metabolism being highest in the list followed by G6PD Deficiency. The commonest presentations were vomiting followed by persistent jaundice.

---

**References**