

PREVALENCE OF CLINICAL SPECTRUM OF INHERITED METABOLIC DISORDERS IN INFANTS AND CHILDREN AT A TERTIARY CARE HOSPITAL IN RAWALPINDI, PAKISTAN

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ABSTRACT

Objective: To determine the frequency of a wide range of clinical presentations of inherited metabolic disorders diagnosed in infants and children at a tertiary care hospital in Rawalpindi, Pakistan.

Study Design: Cross sectional study.

Place and Duration of Study: Pak Emirates Military Hospital, Rawalpindi, from Jun 2015 to Jun 2016.

Methodology: Sixty four children diagnosed with metabolic disorders, reporting to the Pak Emirates Military Hospital Rawalpindi, were enrolled in the study. History was taken with special reference to family history, consanguineous marriage, sibling's death and clinical manifestations. Thorough physical examination was done in every patient to find out the clinical signs present. All the data was recorded on a proforma. SPSS-20 version was used to derive the results and p -value of <0.05 was taken as statistically significant.

Results: In children with metabolic disorders, gastrointestinal manifestation were more significant 78.1% (p -value 0.022). Neurological signs were present in 60.9% (p -value 0.094) while respiratory manifestations were present in 15.6% children (p -value 0.251). fifty three point one percent were males and 46.9% were females. The positive history of other affected children in family was significant (p -value 0.015), along with hypoglycaemia (p -value 0.001).

Conclusion: Pallor, failure to thrive, poor feeding, convulsions, lethargy and hypoglycemia were the most frequent clinical manifestations in children with metabolic disorders.

Keywords: Inherited metabolic disorders, Glycogen storage disorders, Consanguinity, Convulsions.

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INTRODUCTION

Inherited metabolic disorders (IMDs) are a group of genetic disorders in which the body cannot properly turn food into energy¹. These disorders are usually caused by defects in specific proteins (enzymes) that help break down parts of food². The metabolic error is caused due to deficiency of a key enzyme or coenzyme of an intermediary metabolic pathway³. IMDs are frequently misdiagnosed or underdiagnosed because of their nonspecific presentations or some neonates with IMDs may die even before screening⁴.

Inborn error of metabolism should be suspected in neonates with metabolic acidosis, alkalosis or with high serum ammonia level⁵. The term

‘inborn errors of metabolism’ was originally coined by Sir Archibald Garrod at the beginning of the twentieth century. His first publication was on alkaptonuria, he published his most interesting essay entitled ‘The Inborn Factors in Disease’⁶.

Knowledge about inherited metabolic disorders is still in its infancy in Pakistan. Although timely diagnosis of metabolic disorders can help in early institution of medical therapy and can help in successful outcome⁷, there are many issues in our country which are related to under diagnosis of these metabolic disorders including lack of awareness about them in general practitioners and paediatricians, their misdiagnosis, variable presentations of symptoms like poor feeding, lethargy and convulsions which resembles many other diseases like sepsis, lack of adequate

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laboratory facilities for diagnostic confirmation in Pakistan and expensive investigations which many families cannot afford.

A great deal of work has been started in Pakistan, including the facilities to diagnose IMDs. Armed Forces Institute of Pathology (AFIP), Rawalpindi has started doing urine organic acid analysis and Plasma amino acid analysis to diagnose various IMDs. We carried out this study with the hope to find out the most common presentations of metabolic disorders in the paediatric population, so that one can know when to have a high index of suspicion, and when to investigate a neonate or child for IMDs as prevention of death or permanent neurological sequels in patients with these disorders is dependent on early diagnosis and establishment of appropriate therapy⁸.

METHODOLOGY

This was a cross sectional study conducted in paediatrics department, Pak Emirates Military Hospital Rawalpindi after taking permission from hospital ethics committee. Sampling technique used was non-probability consecutive sampling and sample size calculation was done using the WHO sampling calculator. Sixty-four children, who fulfilled the inclusion criteria of having an age range from birth till 12 years and confirmed as having inherited metabolic disorder, falling in any category i.e. disorders of carbohydrate metabolism, disorders of amino acid metabolism, fatty acid oxidation defects, urea cycle defects, organic acidemias, lysosomal storage defects, disorders of electrolyte metabolism etc. were enrolled in the study. All infants and children diagnosed with other congenital infections like TORCH, congenital malaria, tuberculosis, pneumonia, sepsis, neonatal jaundice, hepatitis, connective tissue disorders, malnutrition and infantile leukaemia were excluded. After initial screening laboratory investigations, the diagnosis of specific inherited metabolic disorder was confirmed via respective diagnostic tests to the disorder, including liver biopsy, plasma amino acid analysis by HPLC (High pressure liquid chromatography),

urinary organic acid analysis, thyroid function tests, sweat chloride test, urinary porphobilinogen levels, 17-hydroxyprogesterone levels, which were done at the AFIP. History was taken from the parents of the children with especial acknowledgement to the family history, consanguineous marriage, previous sibling's death or other affected children in the family, education of the parents, socioeconomic status, and their knowledge and understanding about the disease. Detailed physical examination of the children was done to find out any visceromegaly, and other clinical signs and symptoms present in the child with respect to gastrointestinal, respiratory and neurological systems, e.g. poor feeding, lethargy, failure to thrive, recurrent vomiting, diarrhea, tachypnoea, respiratory failure, hypoglycaemia, convulsions, hypotonia, delayed developmental milestones, metabolic acidosis and hepatosplenomegaly were noted. This data was collected on a proforma after taking informed consent from parents. SPSS version 20 was applied to derive results, including frequency and percentages of different symptoms found in the children and *p*-value of <0.05 was taken as statistically significant.

RESULTS

Sixty-four children were selected who fulfilled the inclusion criteria, having an age range since birth till 12 years and diagnosed cases of inherited metabolic disorder. Out of them, 53.1% were males, and 46.9% were females. Twenty one point nine percent cases had a positive history of other affected children in the family (*p*-value

Table-I: Frequency of various factors affecting children with inherited metabolic disorders.

Clinical Manifestations	n (%)	<i>p</i> -value
Consanguinity	57 (89.1%)	0.937
Sibling's death	22 (18.8%)	0.945
Hypoglycaemia	14 (21.9%)	0.001
Metabolic acidosis	03 (4.7%)	0.938

0.015), and the death of siblings was present in 23.4% cases (*p*-value 0.945). Consanguinity among parents was present in 89.1% cases (*p*-value 0.937) table-I.

The most frequent disorder found in our study was the defects in carbohydrate metabolism 25 (39.1%), followed by amino acid metabolism defects 17 (26.6%). Four (6.3%) cases were each of alpha-1 antitrypsin protease deficiency and defects in thyroid hormone synthesis, while 3 (4.7%) cases were of urea cycle defects and defects in electrolyte transport each. There were 2 (3.1%) cases, each of organic acidurias and lysosomal storage defects and 1 (1.6%) case of fatty acid oxidation defects, lactic acidemia, mucopolysaccharidosis and heme biosynthesis defect each (figure).

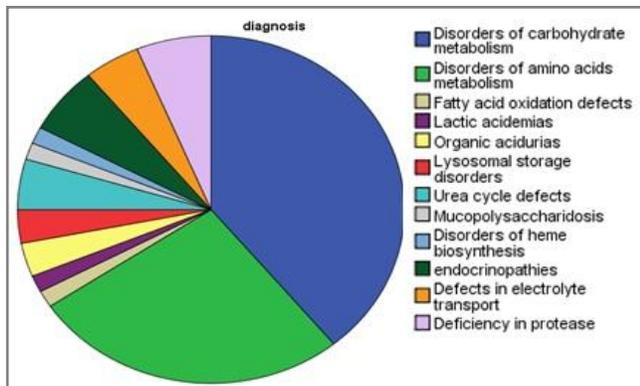


Figure: Frequencies of diverse types of inborn error of metabolism diagnosed in our population.

The gastrointestinal symptoms were noted significant (p -value 0.000) in several types of metabolic disorders. The gastrointestinal manifestations were present in 92% children suffering from the disorders of carbohydrate metabolism and in 76.5% children having amino acid metabolism defects. While the neurological manifestations were present in 64.7% children having amino acid metabolism defects and in 52% children suffering from the disorders of carbohydrate metabolism. Lysosomal storage disorders and organic acidurias presented primarily with gastrointestinal manifestations (100%), while both gastrointestinal and neurological complaints were predominant in lactic acidemias, fatty acid oxidation defects, defects in electrolyte transport and in endocrinopathies. Urea cycle defects and disorders of heme biosynthesis were dominated by neurological manifestations.

Among the gastrointestinal symptoms, the most common complaint was pallor in 31 (48.4%) cases, followed by failure to thrive 26 (40.6%), poor feeding 23 (35.9%), jaundice 22 (34.4%), recurrent vomiting 7 (10.9%), diarrhoea 3 (4.7%) and dehydration 2 (3.1%). Among the neurological symptoms, the most frequent presentation in children with IMD was convulsions 31 (48.4%), followed by lethargy 21 (32.8%), hypotonia 18 (28.1%), delayed developmental milestones 4 (6.3%) and regression of milestones in 2 (3.1%) cases.

Table-II: Frequency of diverse clinical manifestations present in infants and children with metabolic disorders.

Clinical Manifestations	n (%)	p -value
GI Manifestations:	51 (79.7%)	0.022*
Pallor	31 (48.4%)	0.851
Failure to thrive	26 (40.6%)	0.124
Poor feeding	23 (35.9%)	0.522
Jaundice	22 (34.4%)	0.000*
Recurrent vomiting	07 (10.9%)	0.437
Diarrhoea	03 (4.7%)	0.407
CNS Manifestations:	42 (65.6%)	0.094
Convulsions	31 (48.4%)	0.078
Lethargy	21 (32.8%)	0.555
Hypotonia	19 (16.2%)	0.331
Delayed milestones	04 (3.4%)	0.262
Regression of milestones	02 (1.7%)	0.896
Respiratory Manifestations	8 (12.5%)	0.251
Cough	04 (3.4%)	0.019*
Tachypnea	11 (9.4%)	0.251
Respiratory failure	08 (6.8%)	0.246

* p -value <0.05 is considered significant

Cough 4 (6.3%) cases, tachypnoea 10 (15.6%) cases and respiratory failure 8 (12.5%) cases were among the most common respiratory symptoms of metabolic disorders in children. Hypoglycemia was found in 14 (21.9%) cases (p -value 0.001) and metabolic acidosis in 3 (4.7%) cases (p -value 0.938) (table-II).

Among the disorders of carbohydrate metabolism, glycogen storage disorders in 21 (84%) were the most common disorder found in our

population, followed by galactosemia in 4 (16%) patients. Among the amino acid metabolism defects, the most common disorder found was non-ketotichyperglycinemia 7 (41.2%), followed by tyrosinemia 4 (23.5%), hyperphenylalaninemia 3 (17.6%), and 1 (5.9%) case each of maple syrup urine disease, phenylketonuria and alkaptonuria.

DISCUSSION

Knowledge about inherited metabolic disorders is still in its infancy in Pakistan. Although timely diagnosis of metabolic disorders can help in early institution of medical therapy and can help in successful outcome, there are many issues in our country which are related to under diagnosis of these metabolic disorders including lack of awareness about them in general practitioners and paediatricians, their misdiagnosis, variable presentations of symptoms like poor feeding, lethargy and convulsions which resembles many other diseases like sepsis, lack of adequate laboratory facilities for diagnostic confirmation in Pakistan and expensive investigations which many families cannot afford.

A great deal of work has been started in Pakistan, including the facilities to diagnose IMDs. Armed forces institute of Pathology (AFIP), Rawalpindi has started doing urine organic acid analysis and Plasma amino acid analysis to diagnose various IMDs. We carried out this study with the hope to find out the most common presentations of metabolic disorders in the paediatric population, so that one can know when to have a high index of suspicion, and when to investigate a neonate or child for IMDs.

The most common clinical presentations found in our population were convulsions and pallor (48.4%) followed by failure to thrive (40.6%) and poor feeding (35.9%). We found the metabolic acidosis (4.7%), hypoglycemia (21.9%) and history of sibling's death (26.6%). Our results are comparable to those of another study held in Karnataka, India, where 50 children who presented with neurological and metabolic problems were screened for inborn errors of metabolism

and found convulsions (25.7%) the most common presentation, followed by delayed milestones (17.9%), metabolic acidosis (17.2%), failure to thrive (11.7%), lethargy (9.4%), vomiting (9.4%) and hypoglycaemia 9 (10.1%).

History of the sibling's death was found in 26.6% of cases in our study, which was significantly higher as compared to studies in India, where the death of siblings was found in only 6.2% cases⁹, while a study in Syria showed unexplained death of siblings in 50% cases¹⁰.

Methylmalonic acidemias was the most frequent IMD among organic acidemias found in Syrian populations, and the most frequent symptoms were apnea or respiratory distress (65.7%) and vomiting (40%) cases¹⁰. Whereas primary lactic acidemia and organic acidemia were the most frequent disorder, followed by amino acidopathies in a study in India¹¹.

In Slovenia, symptomatic patients with suspected IMD were tested and they diagnosed 168 patients with amino acidopathies and organic acidemias, 5 patients with disorders in fatty acid metabolism, 1 patient with a congenital disorder of glycosylation, 42 patients with Fabry disease and 20 patients with Gaucher disease¹². In Korea, the incidence of IMDs was approximately 1 in 2,235 births¹³, and in Korean population, DUOX2 mutations were found to be a frequent cause of congenital hypothyroidism¹⁴.

A 13-year retrospective cohort study done in Saudi Arabia showed the incidence of IMDs is 169 in 100,000 births. Of these, 121 patients (64.7%) were placed to have small molecule diseases and 66 (35.3%) to take in large molecule diseases. Organic acidemias were the most common small molecule IEMs, while lysosomal storage disorders (LSD) were the most common large molecule diseases and sphingolipidosis were the most common LSD found¹⁵.

Nevertheless, the studies in Pakistan are limited. A study from Children's Hospital, Lahore, enrolled 239 patients. Agreeing to the study in Lahore, parental consanguinity was found in 97% of children, which is almost comparable to

our study in which consanguinity was found in 89.1% of cases. The most frequent presentation found in that population was a metabolic crisis (32.2%) followed by neonatal cholestasis (15.5%) while convulsions (48.4%) and pallor (48.4%) were among the most predominant manifestations in our study. The most frequent disorder found in that study was defects in the carbohydrate metabolism (51%), followed by lipid storage disorders 16 (32.7%) while the most frequent disorder found in our study was defects in the carbohydrate metabolism (39.1%), followed by amino acid metabolism defects (26.6%).

Another study at Shifa International Hospital, Islamabad, enrolled 10 patients who underwent diagnostic work-up of IMD and found out that seizures and coma (50%) were the most common presentations in those children, followed by breathing difficulty (40%) and vomiting 17 (20%). History of early neonatal death in previous siblings was found in 40% of patients, while in our study it was found in 18.8% of cases.

Results conclude that consanguinity is a major contributing factor in our Pakistani population for a specific metabolic disorder, to run in families because most of the IMDs have an autosomal recessive pattern of inheritance¹⁸. During the period of study, interestingly, it was also found that a considerable number of families were having multiple affected children in the same family because of the high rate of consanguineous marriage in our population.

Besides, by comparing the studies conducted in Pakistan, it can be deduced that disorders of the carbohydrate metabolism defects, amino acid metabolism defects and lipid storage disorders are among the commonest metabolic disorders found in our population.

CONCLUSION

Inherited metabolic disorders are quite prevalent in our population belonging to all major categories. Most affected children present with predominant gastrointestinal manifestations, including pallor (48.4%), failure to thrive (40.6%) and poor feeding (35.9%) whereas the

convulsions (48.4%) were the most common neurological manifestation.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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